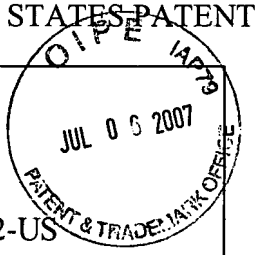
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



In re Application of: Patel et al.

Serial No.: 10/613,698

Attorney Docket No.: 03-40102-US

Filing Date: July 3, 2003

Examiner: Ghali, Isis A D

Art Unit: 1615

DELIVERY SYSTEM FOR TOPICAL MEDICATIONS

APPEAL BRIEF

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The above-identified patent application comes before the United States Patent and Trademark Office Board of Appeals and Interferences from the Final Rejection of Claims 1-18, 34, and 35 by the Examiner in an Official Action mailed October 25, 2006. Pursuant to the Notice of Appeal filed January 9, 2007, set forth below is the Appellant's Brief. A credit card payment form (PTO-2038) is herewith submitted authorizing the payment of $250.00 for payment of the fee under 37 C.F.R. §41.20(b)(2).

The Commissioner is hereby authorized to charge any fees which may be required during the entire pendency of the appeal, or credit any overpayment, to Deposit Account 18-0586.

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I. Real Party in Interest:

The real party in interest in the above-captioned application is Medicis Pharmaceutical Corp. ("Appellant"), a corporation of the State of Delaware, and having a place of business at 8125 N. Hayden Road, Scottsdale, AZ 85258. The application has been assigned to Medicis Pharmaceutical Corp. by the inventors: Bhiku Patel, Mohan Vishnupad, Eugene Gans, and Kuljit Bhatia.

II. Related Appeals and Interferences:

There are no appeals or interferences known to Appellant or Appellant's legal representative which will directly affect or be directly affected by or have a bearing on the Board's decision in this present appeal.

III. Status of Claims:

Claims 1-18, 34, and 35 are pending. Claims 19 and 21-33 were withdrawn and claim 20 was cancelled. Claims 1, 2, 5-18, 34, and 35 were finally rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement, in an Office Action mailed October 25, 2006. Claims 1, 2, 6, 7, and 14-18 were finally rejected under 35 U.S.C. §102(b) as being anticipated by U.S. 5,562,642 ("'642 Patent"). Claims 1, 2, 6, 7, 14, and 16-18 were finally rejected under 35 U.S.C. §102(b) as being anticipated by U.S. 6,183,766 ("'766 Patent"). Claims 3-5, 8-13, 34, and 35 were finally rejected under 35 U.S.C. §103(a) as being unpatentable over the '642 Patent. Claims 3-5, 8-13, 34 and 35 were finally rejected under 35 U.S.C. §103(a) as being unpatentable over the '766 Patent. Claims 4, 5, 34, and 35 were finally rejected under 35 U.S.C. §103(a) as being unpatentable over the '642 Patent in view of the '766 Patent. Claim 15 was finally rejected under 35 U.S.C. §103(a) as being unpatentable over the '766 Patent in view of the '642 Patent. Claims 1-18, 34, and 35 were finally rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. 6,784,145 ("'145 Patent) in view of the '642 Patent. Claims 4, 5, 8-12, 34, and 35 were finally rejected under 35 U.S.C. §103(a) as being unpatentable over the '642 Patent in view of the '145 Patent. Claims 8-12 were finally rejected under 35 U.S.C. §103(a) as being unpatentable over the '766 Patent in view of the '145 Patent. Claims 1-18, 34, and 35 were finally rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. 6,338,855 ("'855 Patent") in view of the '642 Patent. Claims 4, 5, 8-12, 34, and 35 were finally rejected under 35 U.S.C. §103(a) as being unpatentable over the '855 Patent in view of the '642 Patent and further in view of the '145 Patent. Claims 1-18, 34, and 35 are the subject of the present appeal.

IV. Status of Amendments:

No amendments have been filed subsequent to the Final Rejection. All amendments have been entered and are reflected in the claims appendix.

V. Summary of Claimed Subject Matter:

As recited in independent claim 1, the present invention is directed to a drug delivery system comprising a pad, a container, and a liquid composition wherein the composition comprises: (1) an effective amount of one or more insoluble dermatologically active ingredients, and (2) an emulsion vehicle for the insoluble dermatologically active ingredients, wherein the composition has a viscosity low enough for the composition to substantially uniformly absorb onto the pad via capillary action, and high enough to be substantially retained on the pad, not the container. *See* Specification, p. 3, paragraph 11; p. 4, paragraph 13; p. 6, paragraph 28; p. 7, paragraphs 31-32. Claims 6, 7, and 13-18 depend from claim 1 and define the type of emulsion (oil-in-water and water-in-oil), the type of pad (one or more woven materials and one or more non-woven materials), the type of container (comprising a material comprised of metal substantially coated with one or more plastics on at least one surface, and one sheet of the material is heat sealed to a second sheet of the material, and the heat sealed materials contain the pad and the composition without leaking), the addition of one or more soluble dermatologically active ingredients, and the insoluble dermatologically active ingredients as being, for example, benzoyl peroxide, antifungals, prodrugs, cosmeceuticals, herbal medicines, traditional medicines, and cutaneously active cosmetic ingredients. *See* Specification, p. 3, paragraphs 11-12; p. 4, paragraphs 13, 15-16; p. 5, paragraphs 17 and 23; p. 6, paragraphs 24-25 and 28; p. 7, paragraphs 29 and 31-32; p. 14, lines 2-10, 13-19; p. 15, lines 16-24; p. 16, lines 1-2. Claim 2 depends from claim 1 and defines that the viscosity is effective to substantially uniformly deliver the composition to skin when the pad is wiped on the skin. *See* Specification, p. 4, paragraph 14-15; p. 10, paragraph 41. Claims 3-5 and 34-35 ultimately depend from claim 1 and define the active ingredient comprising benzoyl peroxide and benzoyl peroxide comprising particles of less than

about 50 microns; and the active ingredient comprising particles of about 10 to about 150 microns, particles of up to about 300 microns, and particles of less than about 50 microns. *See* Specification, p. 3, paragraph 11, p. 4, paragraph 13 and 16; p. 5, paragraph 23; p. 14, lines 12-17. Claims 8-12 ultimately depend from claim 1 and define the composition having a viscosity of about 500 to about 9000 cps and about 2000 to about 3000 cps measured on a Brookfield viscometer LVT model at about 27°C for 60 seconds and a spindle set for 30 rpm; and a viscosity of about 500 to about 10,000 cps, about 1,900 to about 7,000 cps, and about 4,500 to about 6,500 cps measured on a Brookfield viscometer RVT model with spindle #4 at 20 rpm for 60 seconds at 25°C +-1°C. *See* Specification, p. 6, paragraph 27; p. 11, paragraph 45 and Table 2; p. 12, paragraph 46; p. 4, line 19 – p. 15, line 12.

The claimed invention, among other things, has overcome the problems of the prior art related to the topical delivery of insoluble particulate therapeutic agents by way of a cloth or pad. *See* Specification, p. 3, paragraph 11. As pointed out in Applicant's specification at paragraph 10, pads have been used to topically deliver therapeutic liquids or solutions. See, for example, Stri-Dex® pads, which are a pad delivery system for a salicylic acid solution. *See* Specification, p. 3, paragraph 10. However, insoluble particulate therapeutic agents have posed serious problems for cloth or pad delivery systems. *See* Specification, p. 2-3. For example, insoluble particulate compositions are not uniformly deposited on the pad and the insoluble particulate compositions are not reliably released from the pad and uniformly deposited on the skin during application. *See* Specification, p. 1, paragraphs 3-5. Consequently, the prior art could not know how much or whether any of the dermatologically active ingredient was delivered. This is due in part to the tendency of pads to filter out the particles from the liquid and retain the particles on or in the pad matrix. *Id.* For insoluble particulate therapeutic agents such as benzoyl peroxide, this

can result in the retention of so much of the therapeutic agent on the pad or cloth that a sub-optimal or even sub-therapeutic amount of the agent is delivered to the skin. *See* Specification, p. 2, paragraph 8. The claimed invention solves this problem.

Another problem confronted by the invention has to do with the difficulty in controlling the release of the fluid from the pad. *Id.* The pad must firmly retain the particle-containing fluid on the cloth or pad applicator prior to use, but readily release the particle-containing fluid from the applicator pad or cloth when actually used. A related problem arises when the cloth or pad applicator is stored in a pouch or similar container. For example, creams adhere poorly to pads, but adhere quite well to the container thereby leaving the active ingredients on the walls of the container. *See* Specification, p. 3, paragraph 10. The composition must be retained on the pad and not released to the inside walls of the pouch, since this would leave the composition in the container, unavailable for its intended use (e.g. application to the skin). The invention also solves this problem.

As pointed out in Applicant's specification at paragraph 13, these problems are solved by specified viscosity claimed for the composition. The viscosity of the emulsion must be low enough to allow the fluid to penetrate the pad and to adhere to the pad in preference to the walls of the container, yet viscosity must be high enough to prevent the liquid from draining off the pad (which in the prior art can sometimes leave the insoluble particles behind on the pad). *See* Specification, p. 4, paragraph 13; p. 8, paragraph 33. It has also been found that keeping the particle size of the insoluble material below a certain size also assists in solving these problems. *See* Specification, p. 4, paragraph 13; p. 5, paragraph 23.

VI. Grounds of Rejection to be Reviewed:

Issue 1

Whether claims 1, 2, 5-18, 34, and 35 comply with the written description requirement under 35 U.S.C. §112, first paragraph.

Issue 2

Whether claims 1, 2, 6, 7, and 14-18 are unpatentable under 35 U.S.C. §102(b) over the '642 Patent.

Issue 3

Whether claims 1, 2, 6, 7, 14, and 16-18 are unpatentable under 35 U.S.C. §102(b) over the '766 Patent.

Issue 4

Whether claims 3-5, 8-13, 34, and 35 are unpatentable under 35 U.S.C. §103(a) over the '642 Patent.

Issue 5

Whether claims 3-5, 8-13, 34 and 35 are unpatentable under 35 U.S.C. §103(a) over the '766 Patent.

Issue 6

Whether claims 4, 5, 34, and 35 are unpatentable under 35 U.S.C. §103(a) over the '642 Patent in view of the '766 Patent.

Issue 7

Whether claim 15 is unpatentable under 35 U.S.C. §103(a) over the '766 Patent in view of the '642 Patent.

Issue 8

Whether claims 1-18, 34, and 35 are unpatentable under 35 U.S.C. §103(a) over the '145 Patent in view of the '642 Patent.

Issue 9

Whether claims 4, 5, 8-12, 34, and 35 are unpatentable under 35 U.S.C. §103(a) over the '642 Patent in view of the '145 Patent.

Issue 10

Whether claims 8-12 are unpatentable under 35 U.S.C. §103(a) over the '766 Patent in view of the '145 Patent.

Issue 11

Whether claims 1-18, 34, and 35 are unpatentable under 35 U.S.C. §103(a) over the '855 Patent in view of the '642 Patent.

Issue 12

Whether claims 4, 5, 8-12, 34, and 35 are unpatentable under 35 U.S.C. §103(a) over the '855 Patent in view of the '642 Patent and further in view of the '145 Patent.

VII. Grouping of Claims:

There are 4 groups of claims, which stand or fall separately. Group 1 consists of independent claim 1 and dependent claims 6, 7, 13, 14, 15, 16, 17, and 18. Group 2 consists of dependent claim 2. Group 3 consists of dependent claims 3, 4, 5, 34, and 35. Group 4 consists of dependent claims 8-12.

VIII. Argument:

Issue 1

Whether claims 1, 2, 5-18, 34, and 35 comply with the written description requirement under 35 U.S.C. §112, first paragraph.

The Examiner rejected claims 1, 2, 5-18, 34, and 35 under 35 U.S.C. §112, first paragraph, as purportedly failing to comply with the written description requirement. The Examiner asserts that "no definition [is] given to [the] [] medicines and active ingredients" listed in the specification and "[t]he specification gives no guidance to one of ordinary skill in the art to the insoluble active ingredients." *See* Final Office Action, p. 4-5. The Examiner also asserts that "the expressions 'traditional medicine', [sic] 'herbal medicine', [sic] 'prodrug', [sic] 'cutaneously active cosmetic' and 'insoluble dermatologically active agents' without i.e. partial or complete description does [sic] not convey to one of ordinary skill in the art that applicants were in possession of the claimed subject matter." *Id.* at 5. Further, the Examiner asserts that "the expression 'insoluble drug in an emulsion' does not convey to one of ordinary skill in the art that applicants were in possession of the claimed subject matter." *Id.* at 4. Applicant traverses this rejection because the insoluble dermatologically active agents are described in the specification in such a way as to reasonably convey to one of ordinary skill in the art at the time the application was filed that the Applicant had possession of the claimed invention as required by 35 U.S.C. §112, paragraph 1.

35 U.S.C. §112, first paragraph sets forth in part:

> the specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person

> skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The MPEP summarizes the Federal Circuit's characterization of the written description requirement by stating that, "[a]n applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." MPEP §2163 *citing Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). Further, the MPEP states that "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention." MPEP §2163 *citing Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 68 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998); and *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206 (Fed. Cir. 1991). Thus, the written description requirement is satisfied by describing the identifying characteristics of the claimed invention.

Applicant's claims recite *inter alia* an "insoluble dermatologically active ingredient" and specific types of insoluble dermatologically active ingredients, including prodrugs and cosmeceuticals. *See* Claims 1, 16, and 17. Applicant has satisfied the written description requirement for the claimed invention by describing the invention in terms well-known to those of ordinary skill in the art and by providing the identifying characteristics of the invention as required by the MPEP. The specification states that "[d]ermatologically active ingredients for

topical application to human skin are often insoluble solids (also called particulates) in a media" and that "dermatologically active ingredients in the invention can be any particulate or insoluble drugs including but not limited to drugs, prodrugs, cosmeceuticals, herbal medicines, traditional medicines, and active cosmetic ingredients, that are suitable for topical human use and are suspended and/or dispersed in a vehicle." *See* Specification, p. 1, paragraph 2 and p. 3, paragraph 12, respectively. The specification also provides that the dermatologically active ingredients "may be any drug effective in dermatological prevention or treatment, which is insoluble in the composition and is a particulate." *See* Specification, p. 4, paragraph 15. Additionally, the specification states that the active ingredient:

> may be one or more dermatological drug which is insoluble in the composition, such as without limitation, drugs to treat or prevent acne, fungal infections, yeast infections, rosacea, photodamaged skin, hyperpigmented skin, eczema, allergic or contact dermatitis, seborrheic dermatitis, erythema, or psoriasis; salts or chelates, such as without limitation zinc oxide, iron EDTA, magnesium peroxide, ascorbyl linoleate; abrasives; active acids; active bases, such as without limitation minocycline; neutral actives, such as without limitation hydrocorisone; BPO; antifungals; antibacterials; corticosteroids; keratolytic agents; sulfur; sulfur-containing ingredients; or combinations thereof.

See Specification, p. 4, paragraph 16. It is clear from the specification that Applicant has set forth a description of the invention in terms which are well understood in the art (e.g. the active ingredient being, among other things, "dermatological" and "insoluble"). The specification goes on to state that "insoluble" means "insoluble or weakly or minimally soluble." *See* Specification, p. 1, paragraph 2. The specification also provides examples of "insoluble dermatologically active ingredients," such as BPO, sulfur, and corticosteroids. *See* Specification, p. 4, paragraph 16. These descriptions and the examples all comport with how one of ordinary skill in the art would understand these terms of art. The specification also uses well-known terms of art to

describe the types of insoluble dermatologically active ingredients covered by the claims such as prodrugs and cosmeceuticals. In addition to the well-known terms of art, the specification also uses these terms in such a way to provide context for the terms of art as they relate to the claimed invention, thereby satisfying the written description requirement as explained in MPEP §2163. *See* Specification, p. 1-4.

The Patent and Trademark Office provides examiners with a set of guidelines to follow when examining patent applications for compliance with the written description requirement called the "Revised Interim Written Description Guidelines Training Material" ("Guidelines"). *See* 66 Fed. Reg. 1099, 1099-1111 (January 5, 2001). The Guidelines state that "[t]here is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed." 66 Fed. Reg. 1099, 1105. Further, the Guidelines state that the, "[w]ritten description for a claimed genus may be satisfied . . . by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or chemical properties . . . or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus." *Id.* at 1106. The Guidelines also provide that, "[t]he absence of definitions or details for well-established terms or procedures should not be the basis of a rejection under 35 U.S.C. [§]112, [paragraph] 1, for lack of adequate written description." 66 Fed. Reg. 1099, 1105. Following the teaching of the Guidelines, the written description requirement is satisfied by either identifying the features of the invention, such as its physical and/or chemical properties or by using well-known terms of art.

The Applicant has described the features of the claimed invention as required by the Guidelines by using well-known art recognized terms, such as "dermatologically" and "insoluble," which show the Applicant was in possession of the invention. As discussed above

at pages 14-15, the terms "insoluble" and "dermatologically" are standard chemical terms in the art describing specific chemical properties. Thus, these well-known terms, as well as others used in the specification to describe the claimed invention do not require an explicit definition because they are established terms of art. By using well-known, art recognized terms and placing the well-known terms in context with respect to the present invention Applicant has satisfied the written description requirement as set forth in the Guidelines.

To further support that Applicant has satisfied the written description requirement, during prosecution Applicant provided the Examiner with evidence showing that the terms used to describe the invention are well-known. *See* Evidence Appendix, Tabs 1-8 (Exhibits of Tabs 1-8 were timely submitted to the USPTO on October 4, 2006 in response to the Non-Final Office Action mailed June 22, 2006). For example, the World Health Organization (WHO) provides extensive information on "traditional medicine," as well as "herbal medicines." Specifically, the WHO defines "traditional medicine" as "an ancient medical practice that existed in human societies before the application of modern science to health." *See* Evidence Appendix, Tab 1. The WHO defines "herbal medicine" to include "herbs, herbal materials, herbal preparations and finished herbal products that contain as active ingredients parts of plants, or other plant materials, or combinations." *See* Evidence Appendix, Tab 2. Examples of "traditional medicines" and "herbal medicines" include turmeric and piper nigrum. *See* Evidence Appendix, Tab 3, p. 9 and 17. It is apparent that one of ordinary skill in the art would understand the meaning of "traditional medicine" and "herbal medicine," especially in light of the fact that they have been around far longer than the filing date of the present application.

Additionally, the terms "prodrug," "cosmeceutical," and "active cosmetic ingredients" are also well-known in the art. For example, "prodrugs" are defined as precursors of drugs that

"must undergo a chemical conversion by a metabolic process before becoming active," like 5-aminolaevulinic acid and bis(o-carboxyphenyl ethyl ester) nonanedioate. *See* Evidence Appendix, Tabs 4 and 5. Further, the term "cosmeceutical" was "created in the 1990s from cosm(etic) + (pharma)ceutic" and is defined as "a cosmetic product claimed to have medicinal or drug-like benefits." *See* Evidence Appendix, Tab 6. The term is well-known in the pharmaceutical art. *Id.* Further, a search of the USPTO patent database reveals numerous patents using the art recognized term "cosmeceutical." For example, U.S. Patent No. 6,984,391 is entitled "Composition and Methods for the Delivery of Skin Cosmeceuticals." For additional patents using this well-known term of art, *see* Exhibit Appendix, Tab 7. Applicant has also attached additional references from "Martindale: The complete drug reference" setting forth examples of insoluble active ingredients illustrating that the terms are art recognized. *See* Evidence Appendix, Tab 8. Thus, the terms are known to those of ordinary skill in the art thereby satisfying the requirements set forth by the MPEP and the Guidelines.

Therefore, the Applicant's specification makes it clear that the active ingredient must (1) be dermatological, as recognized in the art and as defined by this chemical property; (2) be insoluble as recognized in the art and as defined by this chemical property; (3) be used to treat and/or prevent skin diseases; and (4) be capable of being topically applied to the skin of humans. *See* claims. Further, the Applicant uses well-known, art recognized terms having well-known meanings. The Applicant also illustrates the context in which the terms are used by providing descriptive illustrations that shows to one of ordinary skill in the art what the claimed invention encompasses and shows Applicant had possession of the claimed invention. The Examiner's assertion that the active ingredient of the invention would encompass a myriad of drugs is unsupported and one of ordinary skill in the art would understand the invention as described and

the active ingredients encompassed by the claims. Based upon the specification in light of the Federal Circuit's characterization of the written description requirement as outlined in the MPEP, the Guidelines set forth by the USPTO, and the actual evidence produced in response to the Examiner's mere assertions, Applicant has exceeded the written description requirement by setting forth a description using well-known art recognized terms and further providing context for those art recognized terms as they relate to the present invention. Therefore, the rejection should be removed.

Issue 2

Whether claims 1, 2, 6, 7, and 14-18 are unpatentable under 35 U.S.C. §102(b) over the '642 Patent.

The Examiner rejected claims 1, 2, 6, 7, and 14-18 under 35 U.S.C. §102(b) as being anticipated by the '642 Patent (the '642 Patent is attached herewith in Evidence Appendix Tab 9). The Examiner has failed to establish that each and every element of the claims is taught by the '642 Patent, and this rejection should be removed.

Applicant agrees with the Examiner's statements throughout prosecution that the '642 Patent does not disclose the claimed viscosity of the composition. *See* Final Office Action, p. 10. In fact, the '642 Patent does not disclose anything about viscosity, including the importance of controlling it.

35 U.S.C. §102(b) sets forth in part:

> A person shall be entitled to a patent unless - . . .
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this

> country, more than one year prior to the date of the application for patent in the United States . . .

Hence, to establish anticipation under 35 U.S.C. §102(b) each and every element of the claimed invention must be taught in the prior art reference. *Verdegaal Bros. c. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). If a reference fails to teach even a single limitation, then the reference does not and cannot anticipate the claimed invention even if the missing limitation could be discoverable through further experimentation. The Federal Circuit has held that:

> a finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

Scripps Clinic & Research Foundation v. Genentech Inc., 18 USPQ2d 1001, 1010 (Fed. Cir. 1991). Further, for a prior art reference to anticipate a claim, the reference must enable a person of ordinary skill in the art to practice the invention. "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003).

According to MPEP §2143.03, examiners are required to examine each and every element of each claim. *See In re Wilson*, 424 F.2d 1382, 1384 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art."). Therefore, all the claim elements, including the viscosity, must be considered. The Examiner has failed to meet this requirement by ignoring the viscosity limitation.

The '642 Patent fails to teach all of the limitations of the claims. Specifically, the viscosity limitation as set forth in the claims is not taught by the '642 Patent or any of the art of record. The Examiner states that "[v]iscosity is inherent to a specific composition" and that "[s]ince the essential elements of the '642 composition are identical to the instant compositions, i.e. composition comprising insoluble active agent and emulsion, the '642 composition is expected to have the same physiochemical properties as the composition set forth in the instant application, such as viscosity of the composition, depending on which insoluble drug and which emulsion are used." *See* Final Office Action, p. 6-7.

The central fallacy of the Examiner's position is the proposition that if two compositions have the same ingredient lists, then they must have the same viscosity. This proposition is offered by the Examiner as a bare assertion. It is unsupported by any documentary or testimonial evidence. On several occasions, the Applicant has requested the Examiner provide a declaration pursuant to 37 C.F.R. §1.104(d)(2) supporting to her assertions, but the Examiner has failed to do so. *See*, e.g., Response filed June 5, 2006, p. 14 and Response filed September 28, 2005, p. 10. This lends further support to the Applicant's position that the Examiner's assertions are not only unsupported, but wrong.

The viscosity of a composition is determined by a number of factors, only one of which is the identity of its ingredients. One of the other important determinants of viscosity is the quantity of each ingredient. As the proportions of the various ingredients changes, so will viscosity. This can be demonstrated by (1) taking notice of common experience, and (2) reference to the art of record in this application.

The Board's attention is directed to the '145 Patent and U.S. 5,821,237 ("'237 Patent"). These two patents are the only art of record that discuss the viscosity of the compositions disclosed. They illustrate that the Examiner's assertion that the claimed viscosity is inherent in a prior art composition because it has the same type of ingredients as the claimed invention is wrong. The '237 Patent's compositions have a viscosity "from about 10,000 to about 300,000 centipoise, more preferably from about 20,000 to about 200,000 centipoise, most preferably from about 50,000 to about 150,000 centipoise." *See* the '237 Patent, Col. 13, lines 25-38. The '145 Patent's compositions have a viscosity of less than 150 centipoise. *See* the '145 Patent, Col. 3, lines 24-30. If the Examiner's assertion concerning viscosity was correct, the compositions of the '237 Patent, the '145 Patent, and the compositions described and claimed in this application would all have the same viscosity, but they do not. These two disclosures completely destroy the Examiner's assertion. They prove that, just because two compositions have the same ingredients, does not mean that they have the same viscosity. The above proof is consistent with common sense, well-known to all.

If one takes a simple mixture of flour and water, and varies the amount of flour added to the same amount of water, the viscosity of each sample will vary. The more flour added to the water the thicker, or more viscous, the mixture becomes. If only a small amount of flour is added the resulting mixture is very thin, almost as if no flour was added to the water at all. On the other hand, if a large amount of flour is added, the mixture becomes thick and paste-like. This further illustrates the error of the Examiner's position that, if the ingredients of compositions are the same, then their viscosities must also be the same.

Having a viscosity that is low enough to allow the fluid to penetrate and adhere to the pad in preference to the wall of the container, and yet high enough to prevent the liquid from draining

off the pad allows the claimed invention to work and overcomes the problems of the prior art. *See* Specification, p. 1-3. The specification specifically highlights the critical nature of the viscosity element. For example, the specification sets forth four tests that were conducted to illustrate the importance of the viscosity of the composition. The first test shows that the active ingredient, benzoyl peroxide, was successfully retained on the pad and not the container, which is critical for allowing the application of the appropriate amount the active ingredient to the treatment site. *Id.* at 9-10. The second test shows that when a pad containing the liquid composition is removed from its container and applied to the face, all the areas of application receive a sufficient amount of the composition. *Id.* at 10-11. The third test shows that when the liquid composition is applied to the face via the pad, the amount of medication the patient receives is within the acceptable levels for topical medication based upon regulatory boards and workers in the art. *Id.* at 11. Finally, the fourth test shows the viscosity of several sample embodiments of the present invention and the method for testing the viscosity of the compositions. *Id.* at 11-13. Based upon the description of the viscosity element of the claims, one of ordinary skill in the art would understand this critical feature of the invention. Thus, not only should the Examiner have considered the viscosity limitation as required, but had she considered the limitation she would have found that neither the '642 Patent, nor any of the other art of record teaches the viscosity limitation of the present claims.

Additionally, the '642 Patent also fails to teach controlling the viscosity to achieve a composition having an insoluble dermatologically active ingredient that is delivered using a pad. According to the claimed invention, the viscosity must be low enough to allow the fluid to penetrate the pad and to adhere to the pad in preference to the walls of the container, yet the viscosity must be high enough to prevent the liquid from draining off the pad (which can

sometimes leave the insoluble particles behind on the pad). The '642 Patent fails to discuss any effect viscosity has on a pad delivery system. Nothing in the '642 Patent teaches that the composition's viscosity would be in the claimed range.

The Examiner also asserts that "US '642 recognized the desire to increase the viscosity of the composition to allow retention of the composition into the substrate, as applicant has done." *See* Final Office Action, p. 6-7. The Examiner does not cite any support for this statement. As discussed above at pages 21-23, the '642 Patent never mentions the viscosity of its compositions, much less mentions that it "recognized the desire to increase the viscosity . . . as applicant has done." The claims cannot be rejected on the basis of imaginary disclosures fabricated by the Examiner.

The present invention has overcome the problems of the prior art by controlling the viscosity of the composition. As pointed out in the specification at paragraph 10, pads have been used to topically deliver therapeutic liquids or solutions such as, Stri-Dex® pads, which are a pad delivery system for a salicylic acid solution. However, particulate therapeutic agents have posed serious problems for cloth or pad delivery systems by, among other things, filtering out the particles from the liquid and retaining the particles on the pad matrix leading to a sub-optimal or even sub-therapeutic amount of the agent being delivered to the skin. The present invention solves this problem as well as has overcome the difficulty in controlling the "release" of the fluid from the pad by controlling the viscosity such that the pad firmly retains the particle-containing fluid on the cloth or pad applicator prior to use, but readily releases the particle-containing fluid from the applicator pad or cloth when actually used. The claimed viscosity allows the fluid to be retained on the pad and not be released to the inside walls of the pouch, since this would leave

the fluid in the container, unavailable for its intended use (e.g. application to the skin). *See* Specification, p. 4, paragraph 13.

Since the '642 Patent does not teach each and every claim limitation of the present invention as discussed hereinabove, the '642 Patent cannot anticipate Claim 1 or claims 2, 6, 7, and 14-18 that depend therefrom. Therefore, this rejection should be removed.

a. Group 2 – Claim 2

In addition to the arguments set forth above, the '642 Patent also does not teach the additional limitations of claim 2 (Group 2). Specifically, the '642 Patent does not describe a viscosity that is effective to substantially uniformly deliver the composition to skin when the pad is wiped on the skin. The '642 Patent not only does not disclose the viscosity of claim 2, it also does not disclose that a viscosity such that the composition is substantially uniformly delivered. Therefore, the '642 Patent cannot anticipate claim 2 because it does not teach all of the limitations of the claims. This rejection should be removed.

Issue 3

Whether claims 1, 2, 6, 7, 14, and 16-18 are unpatentable under 35 U.S.C. §102(b) over the '766 Patent.

The Examiner rejected claims 1, 2, 6, 7, 14, and 16-18 under 35 U.S.C. §102(b) as being anticipated by the '766 Patent (the '766 Patent is attached herewith in Evidence Appendix Tab 10). The Examiner fails to establish that each and every element of the claims is taught by the '766 Patent. Applicant respectfully traverses this rejection for at least the following reasons.

Applicant agrees with the Examiner that the '766 Patent, "does not teach the viscosity, BPO in an emulsion, and the woven material of the claimed invention." *See* Final Office Action, p. 11 (emphasis added). Further, Applicant respectfully submits that the '766 Patent does not teach the particle sizes of the active ingredient as called for by claims 4, 5, 34, and 35. The Examiner states that "[v]iscosity is inherent to a specific composition" and that "[s]ince the essential elements of the '766 composition are identical to the instant compositions, i.e. composition comprising insoluble active agent and emulsion, the '766 composition is expected to have the same physiochemical properties as the composition set forth in the instant application, such as viscosity of the composition, depending on which insoluble drug and which emulsion are used." *See* Final Office Action, p. 8. Contrary to the Examiner's assertions, the viscosity of the composition is not described by the '766 Patent and the viscosity is not inherent. *See* earlier comments on viscosity at p. 21-23. The only discussion of viscosity in the '766 Patent is with respect to specific ingredients of the composition, for example silicones and polyglycerylmethacrylate lubricants, which is not the viscosity of the entire composition. *See* '766 Patent, Col. 2, lines 1-6 and Col. 11, lines 56-62.

The '766 Patent also fails to disclose controlling the viscosity to achieve a composition having an insoluble dermatologically active ingredient that is delivered using a pad. The present invention has overcome the problems of the prior art by controlling the viscosity of the composition. According to the claimed invention, the viscosity must be low enough to allow the fluid to penetrate the pad and to adhere to the pad in preference to the walls of the container, yet the viscosity must be high enough to prevent the liquid from draining off the pad (which can sometimes leave the insoluble particles behind on the pad).

Additionally, the Examiner asserts that the '766 Patent states that "[t]he preferred droplet size of the emulsion is from 0.2 to 200 microns." *See* Final Office Action, p. 8. Not only is this statement wrong, it also has no application to the rejected claims. The '766 Patent teaches that "[t]he average droplet size of the moisturizing phase droplets, which comprise the lipophilic skin moisturizing agent ranges from about 0.005 microns to about 1000 microns, preferably from about 0.1 to about 500 microns, and more preferably from about 0.2 to about 200 microns in diameter." *See* Col. 4, lines 24-29. However, there are no claim limitations pertaining to the droplet size of the emulsion. Rather, the claims of the present invention pertain to the particle size of the insoluble dermatologically active ingredient, which are not addressed by this rejection. *See* claims 4 and 5. The claims are completely clear on this point.

Therefore, the '766 Patent fails to teach each and every element of the claims and thus cannot anticipate claim 1 or claims 2, 6, 7, 14, and 16-18 that depend therefrom. This rejection should be removed.

a. Group 2 – Claim 2

In addition to the arguments set forth above, the '766 Patent also does not disclose the limitations of claim 2 (Group 2). Specifically, the '766 Patent does not disclose that the viscosity is effective to substantially uniformly deliver the composition to skin when the pad is wiped on the skin. The '766 Patent not only fails to teach the viscosity of claim 2, but it also fails to disclose that the viscosity is such that the composition is substantially uniformly delivered. Therefore, the '766 Patent cannot anticipate claim 2 because it does not disclose all of the limitations of the claim. This rejection should be removed.

Issue 4

Whether claims 3-5, 8-13, 34, and 35 are unpatentable under 35 U.S.C. §103(a) over the '642 Patent.

The Examiner rejected claims 3-5, 8-13, 34, and 35 under 35 U.S.C. §103(a) as being unpatentable over the '642 Patent. The Examiner fails to establish a *prima facie* case of obviousness based on the '642 Patent with regard to the present invention.

35 U.S.C. §103(a) sets forth in part:

> [a] patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject mater as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said matter pertains.

To establish a *prima facie* case of obviousness the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP §2142; *Velander v. Garner*, 348 F.3d 1359, 1363 (Fed. Cir. 2003).

According to the Supreme Court, obviousness should be determined by examining (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, and (3) the level of ordinary skill in the prior art. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (February 21, 1966); *see also KSR International, Co. v. Teleflex Inc., et al.*, 127 S. Ct. 1727 (2007). The Supreme Court also identified certain objective evidence of nonobviousness, such as commercial success, long felt but unresolved needs, and failure of others. *Id.*

As discussed above at page 20, MPEP §2143.03 requires examiners to examine the claims as a whole, including each and every element discussed therein. Therefore, all the claim elements, including the viscosity and the particle sizes of the dermatologically active ingredient, must be considered.

The '642 Patent fails to disclose or suggest all the claim limitations in the present application. MPEP §706.02(j). The Examiner states:

> US '642 does not teach the BPO in an emulsion, the claimed particle size and viscosity or the woven material . . .The claimed particle sizes and viscosities do not impart patentability to the claims, absent evidence to the contrary. It is expected that the viscosity of the composition disclosed by the reference having the same ingredients as the claimed composition to have the same viscosity. The art suggests the low viscosity of the liquid by the flowability of the composition in order to be absorbed into the non-woven pad. The woven material does not impart patentability to the claims, absent evidence to the contrary.

See Final Office Action, p. 10 (emphasis added).

Applicant agrees with the Examiner that the '642 Patent does not teach the viscosity, active ingredient particle sizes, BPO in an emulsion, and the woven material of the claimed invention. The Examiner asserts that the claimed particle sizes, viscosities, and woven material do not impart patentability to the claims, absent evidence to the contrary, in order to support her argument that each of these claim elements that are not taught in the '642 Patent are obvious in light of the '642 Patent. By making an unsupported assertion, the Examiner has failed to examine the claims as a whole as required by MPEP §2143.03. In addition to not examining the claims as a whole, the Examiner has failed to establish a *prima facie* case of obviousness.

Taking each claim as a whole and judging the patentability of the claims against the '642 Patent, the claims of the present invention are not rendered obvious. As discussed above at pages 21-24, the '642 Patent is silent as to the viscosity of the composition and the particle sizes of the dermatologically active ingredient. The Examiner's "expectation" that the viscosity of the prior art would be the same as the claimed invention is fatally flawed. *See* discussion at pages 21-24, *supra*, where it is demonstrated that having the same ingredients does not equate to having the same viscosity.

The Examiner also asserts that the "art suggests the low viscosity of the liquid composition as implied by the flowability of the composition in order to be absorbed into the non-woven pad." *See* Final Office Action, p. 10. The Examiner's assertion is not true and misplaced. The "flowability" only, if anything, shows that the pad absorbs the liquid composition, but does not disclose or suggest (1) the viscosity of the claimed invention; (2) the substantial retention of the composition by the pad, not the container; or (3) the substantially uniform delivery of the dermatologically active ingredient to the skin. *See* p. 21-24, *supra*; *see also* the '642 Patent, Col. 8, lines 25-34, Col. 11, lines 27-34. The Examiner provides no support to show that the "low viscosity" extrapolated from the "flowability" of the '642 Patent's composition is the same or even similar to the viscosity of the claimed invention. Neither the Examiner nor the prior art provides any perspective by which to judge the so called "low viscosity." Without anything with which to understand the Examiner's viscosity assertion or the disclosure of the '642 Patent's composition, no one, not even one of ordinary skill in the art, would have any clue as to its meaning.

Since the '642 Patent does not teach the limitations of claim 1 of the present invention, the '642 Patent cannot render claim 1 of the present invention obvious. In addition, Applicant

asserts that dependent claims 2-18, 34, and 35 are likewise in condition for allowance at least by virtue of their ultimate dependence on independent claim 1, but also for their additional limitations, such as specific active ingredient particle sizes and specific viscosities not disclosed or suggested by the '642 Patent.

Even assuming *arguendo* that the Examiner had met the burden of establishing a *prima facie* case of obviousness, Applicant has refuted the obviousness rejection. Applicant has overcome the problems in the prior art and has satisfied the long felt need for a pad delivery system for insoluble dermatologically active ingredients. As discussed above at pages 8-9, prior to the present invention, pad delivery systems for particulate therapeutic agents have posed serious problems. The pads in the prior art often act to filter out the particles from the liquid and retain the particles on the pad matrix resulting in sub-optimal or even sub-therapeutic delivery of the agents. Further, the prior art had problems with the retention of the composition with the particulate therapeutic agent in the pad and release of the composition with the dermatologically active ingredient from the pad. This problem is compounded further when the pad or cloth is stored in a pouch or similar container. Without the viscosity of the present invention, the composition adheres to the walls of the container making the composition unavailable or only minimally available for its intended use. *See* Specification, p. 1, paragraph 5; p. 3, paragraph 11.

Therefore, since the '642 Patent fails to disclose or suggest each and every element of the claims a *prima facie* case of obviousness has not been established and assuming *arguendo* it was, long felt need has been proven overcoming this rejection, which should be removed.

a. Group 3 – Claims 4, 5, 34, and 35

In addition to the arguments set forth above, the '642 Patent also does not disclose the specific active ingredient particle sizes as described in claims 4, 5, 34, and 35 (Group 3). The Examiner offers no support for the assertion that this additional limitation is obvious. Therefore, since the '642 Patent fails to disclose or suggest the viscosity of the claimed invention and the particle sizes of the active ingredient as disclosed in claims 4, 5, 34, and 35, the '642 Patent cannot and does not render the claims obvious and the rejection should be removed. Further, even if a *prima facie* case of obviousness was established, long felt need has been proven overcoming the rejection, which should be removed.

b. Group 4 – Claims 8, 9, 10, 11, and 12

In addition to the arguments set forth above, the '642 Patent also does not disclose the specific viscosities as described in claims 8-12 (Group 4). The Examiner offers no support for the assertion that this additional limitation is obvious. In light of the fact that the '642 Patent fails to even mention the viscosity, much less the specific ranges called for by claims 8-12, the '642 Patent cannot and does not render the claims obvious and the rejection should be removed. Further, even if a *prima facie* case of obviousness was established, long felt need has been proven overcoming the rejection, which should be removed.

Issue 5

Whether claims 3-5, 8-13, 34 and 35 are unpatentable under 35 U.S.C. §103(a) over the '766 Patent.

The Examiner rejected claims 3-5, 8-13, 34, and 35 under 35 U.S.C. §103(a) as being unpatentable over the '766 Patent. The Examiner fails to establish a *prima facie* case of obviousness using the '766 Patent with regard to the present invention. Applicant respectfully traverses this rejection for at least the following reasons.

The '766 Patent fails to teach or suggest all the claim limitations in the present application. MPEP §706.02(j). The Examiner states:

> US '766 does not teach the BPO in an emulsion, the claimed viscosity, or the woven material . . . The claimed viscosities do not impart patentability to the claims, absent evidence to the contrary. It is expected that the viscosity of the composition disclosed by the reference having the same ingredients as the claimed composition to have the same viscosity. The art suggests adding viscosity enhancer to the composition impregnated into [sic] pad. The woven material does not impart patentability to the claims, absent evidence to the contrary.

See Final Office Action, p. 11 (emphasis added).

Applicant agrees with the Examiner that the '766 Patent does not teach the BPO in an emulsion, the claimed viscosity, and the woven material. In order for the Examiner to assert that the claims are obvious in light of the '766 Patent and that each and every claim element is disclosed or suggested by the '766 Patent, she had to assert that the claimed viscosities and woven material do not impart patentability to the claims. Again the Examiner has failed to examine the claims as a whole as required by MPEP §2143.03 despite the Applicant's explanation of the present invention, disclosure in the specification (including the problems in

the prior art overcome by the present invention), and the limitations of the currently pending claims. In addition to not examining the claims as a whole, the Examiner has failed to establish a *prima facie* case of obviousness.

Taking each claim as a whole and judging the patentability of the claims against the '766 Patent, the claims of the present invention are not rendered obvious. As discussed above at pages 25-26, the '766 Patent is silent as to (1) the viscosity of the composition, and (2) the particle sizes of the dermatologically active ingredient. The '766 Patent mentions the viscosity of some of its individual, separate ingredients, but not of the composition when all of its individual ingredients are put together. *See* '766 Patent, Col. 2, lines 1-6 and Col. 11, lines 56-62. The Examiner's "expectation" that the viscosity of the prior art would be the same as the claimed invention lacks support. *See* p. 21-24, *supra*. The Examiner has again failed to put forth prior art showing or a declaration attesting to the fact that the viscosity would be "expected" to be the same as requested by the Applicant pursuant to 37 C.F.R. §1.104(d)(2). *See* p. 21, *supra*. Further, as illustrated above at pages 21-24, having the same ingredients does not equate to having the same viscosity because the amount of each ingredient among other things, contributes to the overall viscosity of the composition.

The Examiner also states that "it is noted that viscosity of a chemical compounds [sic] is a property that cannot be separated from the compounds and compositions having the same ingredients are expected to have the same viscosity" and that "[i]f the emulsion composition of the prior art made from the same materials as the composition of the present claims, then it is expected that the composition of the prior art will have the same viscosity as the instantly claimed composition." *See* Final Office Action, p. 12. This assertion simply restates the fallacious position taken with respect to the viscosity of the compositions of the '642 Patent.

The viscosity of a composition is determined by many factors, including the properties and amounts of each ingredient added. Compositions comprising various ingredients will have a viscosity based upon the amount of each ingredient. Just because two compositions may have the same ingredients, does not mean the two compositions have the same viscosity because the amount of each ingredient of the composition is critical to the overall viscosity of the composition. *See* illustration and discussion of the prior art at p. 21-24, *supra*.

The Examiner cites *In re Aller* with respect to the particle size claim element stating, "they do not impart patentability to the claims since it has been held that where the general conditions of a claim are disclosed in the art, discovering the optimum or workable / [sic] ranges involves only routine skill in the art." *See* Final Office Action, p. 13 *citing In re Aller*, 105 USPQ 233 (CCPA 1955). *In re Aller* is not applicable to this situation. First, in *In re Aller*, the "general conditions" of the invention, e.g. temperature and acid concentration, were all provided in the prior art such that one of ordinary skill in the art could take those conditions and optimize the chemical reaction to achieve a better result. *In re Aller*, 105 USPQ at 235. However, with respect to the Applicant's invention, the "general conditions," namely particle size of the Applicant's claimed invention, are not disclosed in the '766 Patent. The Examiner has confused the emulsion droplet size disclosed in the '766 Patent with being the active ingredient particle size of Applicant's claimed invention in order to attempt to find the "general conditions" of *In re Aller*, which do not exist in the '766 Patent. *See* Final Office Action, p. 8 and 13. Since the general conditions are not disclosed or suggested in the prior art, one of ordinary skill in the art would not know how to routinely optimize the particle size to achieve the present invention.

Second, the patent claims in *In re Aller* were directed to an industrial process, whereas the Applicant's claims are directed to a pharmaceutical product. Third, the *In re Aller* patent was

directed to improvements in the process of making phenol. In contrast, the Applicant's invention is not an improvement, but rather a solution to a long existing problem in the prior art. The Applicant's discovered a way to make a pad delivery system work for insoluble dermatologically active ingredients, which was not accomplished in the prior art. Thus the Applicant's invention produces "a new and unexpected result which is different in kind and not merely in degree from the results of the prior art." *In re Aller*, 105 USPQ at 235.

Therefore, based upon the foregoing, *In re Aller* cannot be invoked because *inter alia*, (1) it only applies when the general conditions of a claim are disclosed in the prior art and the '766 Patent is silent as to particle sizes; and (2) it pertains to improvements to working techniques known in the art. Additionally, *In re Aller* pertains to an improvement on an industrial process which is completely different from the Applicant's invention, which provides a solution to a long standing problem in the prior art.

Since the '766 Patent does not disclose or suggest the claim limitations of claim 1, the '766 Patent cannot render claims 3-5, 8-13, 34, and 35 of the present invention obvious at least by virtue of their ultimate dependence on independent claim 1; but also because of their additional limitations, such as specific active ingredient particle sizes and specific viscosities not disclosed or suggested by the '766 Patent.

Even assuming *arguendo* that the Examiner has met the burden of establishing a *prima facie* case of obviousness, Applicant has rebutted the obviousness rejection. The claimed invention has overcome the problems in the art and has satisfied a long felt need for a pad delivery system for insoluble active ingredients. As discussed above at pages 8-9, prior to the present invention, pad delivery systems for particulate therapeutic agents have posed serious

problems. The pads in the prior art often act to filter out the particles from the liquid and retain the particles on the pad matrix resulting in sub-optimal or even sub-therapeutic delivery of the agents. Further, the viscosity of the prior art prevented the retention of the fluid with the particulate therapeutic agent on the pad and release of the fluid and the agent from the pad. This problem is compounded further when the pad or cloth is stored in a pouch or similar container. Without the viscosity of the present invention, the fluid would adhere to the walls of the container making the composition unavailable for its intended use.

Therefore, since the '766 Patent does not disclose or suggest each and every claim element, a *prima facie* case of obviousness has not been established, and assuming it was, long felt need has been proven overcoming this rejection, which should be removed.

a. Group 3 – Claims 4, 5, 34, and 35

In addition to the arguments set forth above, the '766 Patent also does not disclose the specific active ingredient particle sizes as described in claims 4, 5, 34, and 35 (Group 3). Therefore, since the '766 Patent fails to disclose or suggest the viscosity of the claimed invention and the particle sizes of the active ingredient, the '766 Patent cannot and does not render the claims obvious and the rejection should be removed. Further, even if a *prima facie* case of obviousness was established, long felt need has been proven overcoming the rejection, which should be removed.

b. Group 4 – Claims 8, 9, 10, 11, and 12

In addition to the arguments set forth above, the '766 Patent also does not teach the specific viscosities as described in claims 8-12 (Group 4). In light of the fact that the '766 Patent

fails to disclose or suggest the viscosity of the claimed invention and the specific ranges called for by claims 8-12, the '766 Patent cannot and does not render the claims obvious and the rejection should be removed. Further, even if a *prima facie* case of obviousness was established, long felt need has been proven overcoming the rejection, which should be removed.

Issue 6

Whether claims 4, 5, 34, and 35 are unpatentable under 35 U.S.C. §103(a) over the '642 Patent in view of the '766 Patent.

The Examiner rejected claims 4, 5, 34, and 35 under 35 U.S.C. §103(a) as being unpatentable over the '642 Patent in view of the '766 Patent. Applicant respectfully traverses this rejection for at least the following reasons.

The '766 Patent fails to teach or suggest all the claim limitations in the present application. MPEP §706.02(j). The Examiner states:

> US '642 does not teach the particle size as claimed in claims 4 and 5. US '766 teaches particle sizes of the emulsion are preferred to be between 0.2 and 200 micron. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention to provide the emulsion disclosed by US '642 with particle sizes between 0.2 and 200 micron motivated by the teaching of US '766 that this range of droplet size is preferred for emulsion impregnated in a pad to deliver active agents to the skin, with reasonable expectation of having emulsion having droplet sizes of 0.2 and 200 micron impregnated in a pad that deliver active ingredients to the skin with great success.

See Final Office Action, p. 13.

Applicant agrees with the Examiner that the '642 Patent does not teach the active ingredient particle sizes as claimed in claims 4 and 5, and that the '642 Patent and the '766

Patent do not teach the claimed viscosity of the composition. *See* Final Office Action, p. 10-11 and 13.

The '642 Patent and '766 Patent fail to disclose or suggest the specific particle sizes of the active ingredient (e.g. BPO) of claims 4 and 5. The '766 Patent also does not disclose or suggest "particle sizes of the emulsions are preferred to be between 0.2 and 200 microns" as asserted by the Examiner. Rather, the '766 Patent teaches that "[t]he average droplet size of the moisturizing phase droplets, which comprise the lipophilic skin moisturizing agent ranges from about 0.005 microns to about 1000 microns, preferably from about 0.1 to about 500 microns, and more preferably from about 0.2 to about 200 microns in diameter." *See* Col. 4, lines 24-29. These droplets are not particles of the active ingredient. The Examiner's argument is misplaced and has no bearing on the present invention.

The Examiner also argues that

> the particles [sic] size of the active agent is the only difference between the cited references and the present claims, and it would have been obvious to one having ordinary skill in the art at the time the invention was made to select the particle size, since it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable / [sic] ranges involves only routine skill in the art.

See Final Office Action, p. 14. This argument is also misplaced and has no bearing on the present invention.

As discussed above at page 27, the '766 patent may discuss the droplet size of the moisturizing phase of the emulsion; however none of Applicant's claims pertain to the droplet size of the moisturizing phase of the emulsion. Rather, the claims of the present invention pertain to the particle size of the insoluble dermatologically active ingredient. The Examiner

fails to understand this difference. Further, the size ranges assert by the Examiner as teaching the particle size are not of the active ingredient as claimed by the Applicant, but rather to an entire phase of a total composition.

The references are silent as to the viscosity and the active ingredient particle sizes. The '642 Patent and the '766 Patent fail to even mention the viscosity or active ingredient particle sizes, much less the specific ranges called for by Applicant's claims 4, 5, 34, and 35. Further, there is no optimum or workable range to achieve from the disclosure because the references do not teach anything about viscosity or particle size.

The particle sizes of the active ingredient are not the only differences between the cited references and the presently claimed invention. As discussed above at pages 21-24 and 26-27, the '642 Patent and the '766 Patent fail to disclose or suggest the claimed viscosity. Further, the references fail to disclose or suggest controlling the viscosity to achieve a composition having an insoluble dermatologically active ingredient that is delivered using a pad such that the active ingredient is not filtered by the pad.

The Examiner again cites *In re Aller* arguing that the particle size claim element does not impart patentability because "where the general conditions are disclosed in the art, discovering the optimum or workable / [sic] ranges involves only routine skill in the art." *See* Final Office Action, p. 14 *citing In re Aller*, 105 USPQ 233 (CCPA 1955). As discussed above at pages 34-36, *In re Aller* does not apply to this situation for several reasons, including the fact that "general conditions," namely particle size, are not disclosed in the '642 Patent and the '766 Patent. *See* p. 34-36, *supra*. The Examiner has acknowledged this shortcoming of the references. *See* Final Office Action, p. 13 and discussion at p. 34-36, *supra*. Since the general conditions are not

disclosed in the prior art one of ordinary skill in the art would not know how to routinely optimize the particle size to achieve the present invention.

Therefore, as discussed above, *In re Aller* cannot be invoked because *inter alia*, (1) it only applies when the general conditions of a claim are disclosed in the prior art and the '642 Patent and the '766 Patent are silent as to particle size; and (2) it pertains to improvements to working techniques known in the art. Additionally, *In re Aller* pertains to an improvement on an industrial process which is completely different from the Applicant's invention, which provides a solution to a long standing problem in the prior art.

Even assuming *arguendo* that the Examiner had met the burden of establishing a *prima facie* case of obviousness, Applicant has rebutted the obviousness rejection. Applicant has overcome the problems in the prior art and has satisfied the long felt need for a pad delivery system for insoluble active ingredients. As discussed above at pages 8-9, prior to the present invention, pad delivery systems for particulate therapeutic agents have posed serious problems. The pads in the prior art often act to filter out the particles from the liquid and retain the particles on the pad matrix resulting in sub-optimal or even sub-therapeutic delivery of the agents. Further, the viscosity of the prior art prevented the retention of the fluid with the particulate therapeutic agent in the pad and release of the fluid and the agent from the pad. This problem is compounded further when the pad or cloth is stored in a pouch or similar container. Without the viscosity of the present invention, the fluid adheres to the walls of the container making the composition unavailable for its intended use.

Therefore, since the '642 Patent and the '766 Patent, even if *arguendo* they could be properly combined, do not disclose or suggest each and every claim element, the references do

not render the claimed invention obvious and the rejection should be removed. Further, even if a *prima facie* case of obviousness was established, long felt need has been proven overcoming the rejection, which should be removed.

Issue 7

Whether claim 15 is unpatentable under 35 U.S.C. §103(a) over the '766 Patent in view of the '642 Patent.

The Examiner rejected claim 15 under 35 U.S.C. §103(a) as being unpatentable over the '766 Patent in view of the '642 Patent. Applicant respectfully traverses this rejection for at least the following reasons.

Claim 15 is dependent on claim 1. As discussed above, the '766 and the '642 Patents do not teach all of the claim elements nor make the claimed invention obvious. Specifically, the references fail to teach or suggest the claimed viscosity. *See* p. 21-24 and 26-37, *supra*. Therefore, even if the '766 Patent and the '642 Patent were properly combined, the Examiner has not met her burden for establishing that claim 15 is obvious in light of the '766 Patent and the '642 Patent and the rejection should be removed. Further, even if a *prima facie* case of obviousness was established long felt need has been proven overcoming the rejection. *See* p. 36, *supra*.

Issue 8

Whether claims 1-18, 34, and 35 are unpatentable under 35 U.S.C. §103(a) over the '145 Patent in view of the '642 Patent.

The Examiner rejected claims 1-18, 34, and 35 under 35 U.S.C. §103(a) as being unpatentable over the '145 Patent in view of the '642 Patent (the '145 Patent is attached herewith in Evidence Appendix Tab 11). The Examiner fails to establish a *prima facie* case of obviousness using the '145 Patent in view of the '642 Patent with regards to the present invention. Applicant respectfully traverses this rejection for at least the following reasons.

As discussed above at pages 19 and 29, the Examiner has admitted that the '642 Patent does not teach the claim elements of viscosity, particle size, BPO in an emulsion, and woven material.

The Examiner's assertion that viscosity, particle size, and woven material are "inherent" and do not impart patentability is plainly wrong. Contrary to the Examiner's assertions, the claimed viscosity is not inherent and the viscosity of the composition is not taught in the '642 Patent. *See* p. 21-24, *supra*. The '642 Patent also fails to disclose or suggest controlling the viscosity to achieve a composition having an insoluble dermatologically active ingredient that is delivered using a pad. According to the claimed invention, the viscosity must be low enough to allow the fluid to penetrate the pad and to adhere to the pad in preference to the walls of the container, yet the viscosity must be high enough to prevent the liquid from draining off the pad (which can sometimes leave the insoluble particles behind on the pad). *See* Specification, p. 3-4.

The Examiner asserts that the '145 Patent teaches, among other things, the viscosity and active ingredient particle sizes of the claimed invention. The Examiner misreads the '145 Patent.

The '145 Patent teaches a composition having a viscosity below 150 mPa.s in order to be suitable to impregnate the substrate. This viscosity is well below the range of the claimed invention. A conversion of the 150 mPa.s to centipoise (cps) yields 150 cps at room temperature (25° C) with a Rheomat RM 180 machine, using a No. 1 spindle. *See* Response to Office Action mailed June 22, 2006, p. 19, line 9 – p. 20, line 14. With a viscosity below 150 cps, this reference fails miserably to teach the viscosity of the claimed invention. For example, claim 8 calls for a viscosity range of about 500 to about 9000 cps. The viscosity taught in the '145 Patent is significantly below that of the claimed invention. The low viscosity of the '145 Patent would result in the active ingredient being filtered by the pad and not being applied to the treatment site. Thus, the '145 Patent actually teaches away from the viscosity of the present invention because a viscosity of 150 cps is substantially below the claimed viscosities and fails to solve the retention and application problems in the prior art. Further, even if the viscosity of the '145 Patent is the same as the viscosity of the claimed invention, the Examiner has not provided any art to show that this is true. One should also note that the '145 Patent does not use the viscosity measurement techniques called for by claims 8-12.

The '145 Patent is also silent with respect to particle size of the active ingredient. The only discussion of size is with respect to the substrate and the globules of the fatty phase in an oil-in-water emulsion, which are not the particle size of the dermatologically active ingredient. *See* '145 Patent, Col. 7, lines 62-65 and Col. 8, lines 28-32. Thus, the '145 Patent fails to disclose not only the particle size of the dermatologically active ingredient, but the claimed viscosity as well.

Even assuming *arguendo* that the Examiner has met the burden of establishing a *prima facie* case of obviousness, Applicant has rebutted the obviousness rejection. Applicant has overcome the problems in the prior art and has satisfied the long felt need for a pad delivery system for insoluble active ingredients. As discussed above at pages 8-9, prior to the present invention, pad delivery systems for particulate therapeutic agents have posed serious problems. The pads in the prior art often act to filter out the particles from the liquid and retain the particles on the pad matrix resulting in sub-optimal or even sub-therapeutic delivery of the agents. *See* Specification, p. 1-2. Further, the viscosity of the prior art prevented the retention of the fluid with the particulate therapeutic agent in the pad and release of the fluid and the agent from the pad. This problem is compounded further when the pad or cloth is stored in a pouch or similar container. Without the viscosity of the present invention, the fluid adheres to the walls of the container making the composition unavailable for its intended use.

Therefore, since the '145 Patent and the '642 Patent, even if properly combined, do not disclose or suggest each and every claim element, the references do not render the claimed invention obvious and the rejection should be removed. Further, even if a *prima facie* case of obviousness was established, long felt need has been proven overcoming this rejection, which should be removed.

a. Group 2 – Claim 2

In addition to the arguments set forth above, the '145 Patent and the '642 Patent also do not teach the limitations of claim 2 (Group 2). Specifically, the '145 Patent and the '642 Patent fail to disclose or suggest a viscosity effective to substantially uniformly deliver the composition to skin when the pad is wiped on the skin. The '145 Patent in view of the '642 Patent not only

fails to disclose or suggest the viscosity of claim 2, they also fail to disclose or suggest a viscosity such that the composition is substantially uniformly delivered. Therefore, even if the '145 Patent and the '642 Patent were properly combined, they do not render claim 2 obvious because they do not disclose or suggest all of the claim limitations. Further, even if a *prima facie* case of obviousness was established, long felt need has been proven overcoming the rejection, which should be removed.

b. Group 3 – Claims 4, 5, 34, and 35

In addition to the arguments above, the '145 Patent also fails to teach the specific active ingredient particle sizes of claims 4, 5, 34, and 35 (Group 3). The Examiner cites to a part of the '145 Patent that discusses the globule size of the moisturizing phase of the emulsion, which is not the particle size of the insoluble dermatologically active ingredient. The '145 Patent does not disclose the particle size for insoluble dermatologically active ingredients, including BPO. Therefore, even if the '145 Patent and the '642 Patent were properly combined, they do not render the claimed invention obvious because they do not disclose or suggest each and every claim element. Further, even if a *prima facie* case of obviousness was established, it has been rebutted by the Applicant's showing that the invention meets long felt but unmet needs (e.g. release from the container, release of particles from the pad to the skin, and more uniform deposition of the particulate active ingredient), which should be removed.

c. Group 4 – Claims 8, 9, 10, 11, and 12

In addition to the arguments set forth above, the '145 Patent and the '642 Patent also do not disclose or suggest the specific viscosities using specific viscometers as described in claims 8-12 (Group 4). Therefore, even if the '145 Patent and the '642 Patent were properly combined,

they do not render the claimed invention obvious because they fail to disclose or suggest the viscosity, much less the specific ranges called for by claims 8-12 (Group 4). Further, even if a *prima facie* case of obviousness was established, long felt need has been proven overcoming the rejection, which should be removed.

Issue 9

Whether claims 4, 5, 8-12, 34, and 35 are unpatentable under 35 U.S.C. §103(a) over the '642 Patent in view of the '145 Patent.

The Examiner rejected claims 4, 5, 8-12, 34, and 35 under 35 U.S.C. §103(a) as being unpatentable over the '642 Patent in view of the '145 Patent. Applicant respectfully traverses this rejection for at least the following reasons.

As discussed above at pages 21-24 and 43-44, the '642 Patent and the '145 Patent fail to teach the claimed active ingredient particle sizes and the claimed viscosity. It is inconsequential whether the '642 Patent teaches droplet sizes of an emulsion being between 50-1000 microns because the claims do not (and never did) have any limitations pertaining to the droplet size of the emulsion. Rather, the pending claims pertain to the particle size of the dermatologically active ingredient. For example, claim 4 explicitly refers to the particle size of BPO. Further, the '145 Patent teaches away from the viscosity of the claimed invention because as discussed above at pages 21-24 and 43-44, a viscosity of 150 cps is significantly below the viscosities called for by the pending claims.

Further, the Examiner's assertion that the claimed invention is a matter of discovering the optimum or workable ranges because the general conditions of the claims are provided in the

prior art is misplaced. As discussed above at pages 34-36, *In re Aller* does not apply to this situation for several reasons, including the fact that "general conditions," namely particle size, are not disclosed in the '642 Patent and the '145 Patent. *See* discussion above at p. 34-36 and 43-44. The Examiner has acknowledged this shortcoming of the references. *See* Final Office Action, p. 17 and discussion above at p. 34-36. Since the general conditions are not disclosed in the prior art one of ordinary skill in the art would not know how to routinely optimize the particle size to achieve the present invention.

Therefore, as discussed above at pages 34-36, *In re Aller* cannot be invoked because *inter alia*, (1) it only applies when the general conditions of a claim are disclosed in the prior art and the '766 Patent is silent as to particle size; and (2) it pertains to improvements to working techniques known in the art. Additionally, *In re Aller* pertains to an improvement on an industrial process which is completely different from the Applicant's invention, which provides a solution to a long standing problem in the prior art.

The present invention also solves a long felt need of a pad delivery system for insoluble active ingredients that treats the site of application. *See* p. 8-9 and 31, *supra*. Therefore, even if the '642 Patent and the '145 Patent were properly combined, they fail to establish a *prima facie* case of obviousness because they fail to disclose or suggest each and every element of the claims and assuming it was, long felt need has been proven overcoming this rejection, which should be removed.

a. Group 3 – Claims 4, 5, 34, and 35

In addition to the arguments set forth above, the '642 Patent and the '145 Patent also do not teach the specific active ingredient particle sizes as described in claims 4, 5, 34, and 35

(Group 3). The Examiner cites to a part of the '145 Patent that discusses the globule size of the emulsion, but the globule size of the emulsion is not the particle size of the insoluble dermatologically active ingredient. The '145 Patent does not disclose the particle size for insoluble dermatologically active ingredients, including BPO. Therefore, even if the '642 Patent and the '145 Patent were properly combined, they do not render the claimed invention obvious because they do not disclose or suggest each and every claim element and the rejection should be removed. Further, even if a *prima facie* case of obviousness was established, long felt need has been proven overcoming the rejection, which should be removed.

b. Group 4 – Claims 8, 9, 10, 11, and 12

In addition to the arguments set forth above, the '642 Patent and the '145 Patent also do not teach the specific viscosities using specific viscometers as described in claims 8-12 (Group 4). Therefore, even if the '145 Patent and the '642 Patent were properly combined, they fail to render the claims obvious because they do not disclose or suggest the viscosity, much less the specific ranges called for by claims 8-12. Further, even if a *prima facie* case of obviousness was established, long felt need has been proven overcoming the rejection, which should be removed.

Issue 10

Whether claims 8-12 are unpatentable under 35 U.S.C. §103(a) over the '766 Patent in view of the '145 Patent.

The Examiner rejected claims 8-12 under 35 U.S.C. §103(a) as being unpatentable over the '766 Patent in view of the '145 Patent. The Examiner fails to establish a *prima facie* case of

obviousness using the '766 Patent in view of the '145 Patent with regards to the present invention. Applicant respectfully traverses this rejection for at least the following reasons.

The '766 Patent and the '145 Patent fail to disclose or suggest all the claim limitations in the present application. MPEP §706.02(j). The Examiner states:

> US '766 does not teach the viscosity of the emulsion, which is taught by US '145. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide an article comprising [sic] nonwoven substrate impregnated with active agent in an emulsion to below 150 mPa.s as disclosed by US '145, motivated by the teaching of US '145 that this viscosity is suitable to allow the emulsion to impregnate the substrate, with reasonable expectation of having a packaged article comprising [sic] substrate impregnated with [sic] emulsion having viscosity [sic] less than 150 mPa.s wherein the composition impregnates the substrate and [sic] retained in there successfully till [sic] time of use.

See Final Office Action, p. 18.

Applicant agrees with the Examiner that the '766 Patent does not teach the viscosity of the emulsion and respectfully submits that the '145 Patent does not disclose or suggest the claimed viscosity. *See* p. 33 and 43, *supra*. As discussed above at pages 43-44, the '145 Patent actually teaches away from the viscosity of the present invention because the '145 Patent teaches a viscosity of 150 cps which is substantially below the claimed viscosities.

Further, the '145 Patent fails to solve the retention and application problems of the prior art. *See* p. 8-9 and 43-45, *supra*. As discussed above at pages 8-9, the viscosity is a critical feature of the invention that allows for the fluid to penetrate the pad and to adhere to the pad in preference to the walls of the container yet prevent the liquid from draining off the pad, which can sometimes leave the insoluble particles behind on the pad resulting in a sub-optimal or even a sub-therapeutic amount of the agent being delivered to the skin. The viscosity of the '145

Patent would result in the same problems seen in the prior art, including the composition adhering to the walls of the container and the particulate therapeutic agent being filtered by the pad matrix, which the present invention has overcome by controlling the viscosity of the composition.

Again, the Examiner cites *In re Aller* and asserts that the claimed invention is a matter of discovering the optimum or workable ranges because the general conditions of the claims are provided in the prior art, which is misplaced. *See* p. 34-36, *supra*. The '766 Patent and '145 Patent do not provide the general conditions of the viscosity because neither reference teaches the viscosity of the claimed invention. Thus, the present invention is not a matter of finding the optimum or workable range because no guidance is provided in the prior art references. Further, the present invention satisfies a long felt need of a pad delivery system for insoluble active ingredients. *See* p. 8-9 and 36, *supra*.

Therefore, even if the '766 Patent and the '145 Patent were properly combined, they fail to establish a *prima facie* case of obviousness because their combination does not disclose or suggest each and every claim element of claims 8-12 (Group 4). Moreover, even if their combination did result in all of the elements of the claims, the non-obviousness is amply demonstrated by the long-felt need for this invention. This rejection should be removed.

Issue 11

Whether claims 1-18, 34, and 35 are unpatentable under 35 U.S.C. §103(a) over the '855 Patent in view of the '642 Patent.

The Examiner rejected claims 1-18, 34, and 35 under 35 U.S.C. §103(a) as being unpatentable over the '855 Patent in view of the '642 Patent (the '855 Patent is attached herewith in Evidence Appendix Tab 12). Applicant respectfully traverses this rejection for at least the following reasons.

Applicant agrees with the Examiner that "US '855 does not teach the article in a container, or particle sizes or the viscosity of the composition." *See* Final Office Action, p. 19 (emphasis added).

The Examiner asserts that the container is found in the '642 Patent and again asserts that the claimed active ingredient particle sizes and viscosity do not impart patentability to the claims "because the art recognized the desire to have viscosity of the impregnated composition enough to retain the composition in the pad, absent evidence to the contrary." *See* Final Office Action, p. 20. Applicant respectfully disagrees.

As discussed above at pages 21-24 and 29, the Examiner's argument that active ingredient particle sizes and viscosity do not impart patentability is unsupported and is made without citing to prior art or providing a declaration pursuant to Applicant's numerous requests under 37 C.F.R. §1.104(d)(2). The fact that a pad may be impregnated with some sort of composition does not show the claimed invention, which includes a carefully defined composition having a viscosity within a certain range. As previously discussed at pages 8-9, the

Applicant has pointed out the problems associated with delivery of insoluble active ingredients with applicator pads, which the present invention has overcome. For example, the pads often act to filter out the particles from the liquid and retain the particles on the pad matrix. *See* Specification, p. 1-3. For insoluble particulate therapeutic agents, such as BPO, this can result in the retention of so much of the therapeutic agent in the pad or cloth that a sub-optimal or even sub-therapeutic amount of the agent is delivered to the skin. *Id.* Another problem overcome by this invention has to do with the difficulty in controlling the "release" of the fluid from the pad. *Id.* The present invention firmly retains the particle-containing fluid on the cloth or pad applicator prior to use, but readily release the particle-containing fluid from the applicator pad or cloth when actually used.

In contrast to the claimed invention, the '855 Patent pertains to a "substantially dry, disposable, personal cleansing article useful for both cleansing the skin or hair and delivering skin care actives to the skin or hair." *See* Abstract (emphasis added). The cleansing article works by application of water to the article by the user and working up a lather prior to application. *See* Abstract. This flies in the face of the present invention and the '855 Patent actually teaches away from the presently claimed invention. The claimed invention has a pad that holds a liquid composition such that the insoluble dermatologically active ingredient is absorbed onto the pad and retained on the pad. The claimed drug delivery system comprises a pad with a liquid composition that is an emulsion and is ready for application upon removal from the container.

The '642 Patent does not make up for the deficiencies of the '855 Patent. The '642 Patent does not disclose or suggest the claimed viscosity or the active ingredient particle sizes of the insoluble dermatologically active ingredient. *See* p. 21-24, *supra*. Further, there is no

motivation to combine these references because the '855 Patent teaches a pad that requires the addition of water and working the water and ingredients in the pad into a lather and the '642 teaches a pad with the composition already on the pad ready for application once removed from the package.

Even assuming *arguendo* that the Examiner has met the burden of establishing a *prima facie* case of obviousness, Applicant has rebutted the obviousness rejection. Applicant has overcome the problems in the prior art and has satisfied the long felt need for a pad delivery system for insoluble active ingredients. As discussed above at pages 8-9, prior to the present invention, pad delivery systems for particulate therapeutic agents have posed serious problems. The pads in the prior art often act to filter out the particles from the liquid and retain the particles on the pad matrix resulting in sub-optimal or even sub-therapeutic delivery of the agents. Further, the viscosity of the prior art prevented the retention of the fluid with the particulate therapeutic agent in the pad and release of the fluid and the agent from the pad. This problem is compounded further when the pad or cloth is stored in a pouch or similar container. Without the viscosity of the present invention, the fluid adheres to the walls of the container making the composition unavailable for its intended use.

Therefore, even if the '855 Patent and the '642 Patent were properly combined, they do not render the claims obvious because they fail to disclose or suggest each and every claim element and there is no motivation to combine the references. Further, even if a *prima facie* case of obviousness was established, long felt need has been proven overcoming the rejection, which should be removed.

a. Group 2 – Claim 2

In addition to the arguments set forth above, the '855 Patent and the '642 Patent also do not teach the limitations of claim 2 (Group 2). Specifically, even if the '855 Patent and the '642 Patent were properly combined they do not disclose or suggest the viscosity is effective to substantially uniformly deliver the composition to skin when the pad is wiped on the skin. The '855 Patent and the '642 Patent not only fail to teach the viscosity of claim 2, they also fail to teach that the viscosity is such that the composition is substantially uniformly delivered. Therefore, even if the '855 Patent and the '642 Patent were properly combined they fail to render the claims obvious because they do not teach all of the limitations of the claim. Moreover, even if their combination did result in all of the elements of the claims, the non-obviousness of the combination is amply demonstrated by the long-felt need for this invention, which should be removed.

b. Group 3 – Claims 4, 5, 34, and 35

In addition to the arguments set forth above, the '855 Patent and the '642 Patent also fail to disclose or suggest the specific active ingredient particle sizes as disclosed in claims 4, 5, 34, and 35 (Group 3). Therefore, even if the '855 Patent and the '642 Patent were properly combined, they fail to render the claims obvious because they fail to disclose or suggest the particle sizes of the active ingredient. Moreover, even if their combination did result in all of the elements of the claims, the non-obviousness of the combination is amply demonstrated by the long-felt need for this invention, which should be removed.

c. Group 4 – Claims 8, 9, 10, 11, and 12

In addition to the arguments set forth above, the '855 Patent and the '642 Patent also fail to disclose or suggest the specific viscosities as described in claims 8-12 (Group 4). Therefore, even if the '855 Patent and the '642 Patent were properly combined they fail to render the claims obvious because they fail to disclose or suggest the viscosity, much less the specific ranges called for by claims 8-12. Moreover, even if their combination did result in all of the elements of the claims, the non-obviousness of the combination is amply demonstrated by the long-felt need for this invention, which should be removed.

Issue 12

Whether claims 4, 5, 8-12, 34, and 35 are unpatentable under 35 U.S.C. §103(a) over the '855 Patent in view of the '642 Patent and further in view of the '145 Patent.

The Examiner rejected claims 4, 5, 8-12, 34, and 35 under 35 U.S.C. §103(a) as being unpatentable over the '855 Patent in view of the '642 Patent and further in view of the '145 Patent. The Examiner fails to establish a *prima facie* case of obviousness using the '855 Patent in view of the '642 Patent and further in view of the '145 Patent with regards to the present invention. Applicant respectfully traverses this rejection for at least the following reasons.

Applicant agrees with the Examiner that the "combined teaching of US '855 and US '642 does not teach the exact active ingredient particle sizes and viscosities as claimed by the applicants." *See* Final Office Action, p. 22.

Applicant also respectfully submits that the Examiner's argument that the '145 Patent "teaches the same ranges of particles sizes and viscosity of the composition because and [sic]

teaches that these parameters are suitable for impregnating the composition into a substrate" is wrong. Again, as discussed above, the '855, '642, and '145 Patents fail to disclose or suggest the claimed active ingredient particle sizes and the claimed viscosity. *See* p. 21-24, 29-31, and 42-54, *supra*. The particle size element of the claims refers to the size of the insoluble dermatologically active ingredient; for example, claim 4 explicitly refers to the particle size of BPO (and always did). Contrary to the Examiner's assertions, the '145 Patent does not teach the same ranges of particles sizes or the viscosity of the composition. *See* p. 43-44, *supra*. Further, one cannot conclude that the disclosed emulsion particle sizes and significantly low viscosity of the '145 Patent teach the claimed invention merely because they are suitable for impregnating the composition into a substrate. Further, one of ordinary skill in the art armed with the prior art of record would not be able to or be motivated to make the present invention because the teachings are so lacking. Once again, the present invention overcomes the problems of the prior art, e.g., substantially uniform absorption onto the pad and substantially uniform delivery of the dermatologically active ingredient from the pad to the site of application, thereby satisfying a long felt need. *See* p. 31, *supra*. Therefore, even if the '855 Patent, the '642 Patent, and the '145 Patent were properly combined, they fail to render the claims obvious because they do not teach all of the limitations of the claim. Further, even if a *prima facie* case of obviousness was established, long felt need has been proven overcoming the rejection, which should be removed.

a. Group 3 – Claims 4, 5, 34, and 35

In addition to the arguments set forth above, the '145 Patent also fails to teach the specific particle size of the insoluble dermatologically active ingredient of claims 4, 5, 34, and 35 (Group 3). The Examiner cites to a part of the '145 Patent that discusses the globule size of the emulsion, but the globule size of the emulsion is not the particle size of the insoluble

dermatologically active ingredient. The '145 Patent does not disclose the particle size for insoluble dermatologically active ingredients, including BPO. Therefore, even if the '855 Patent, the '642, and the '145 Patent were properly combined they do not render the claims obvious because they do not disclose or suggest each and every claim element. Further, even if a *prima facie* case of obviousness was established, long felt need has been proven overcoming the rejection, which should be removed.

b. Group 4 – Claims 8, 9, 10, 11, and 12

In addition to the arguments set forth above, the '855 Patent, the '145 Patent, and the '642 Patent also do not teach the specific viscosities using specific viscometers as described in claims 8-12 (Group 4). Therefore, even if the '855 Patent, the '145 Patent, and the '642 Patent were properly combined they fail to render the claims obvious because they fail to disclose or suggest the viscosity, much less the specific ranges called for by claims 8-12. Further, even if a *prima facie* case of obviousness was established, long felt need has been proven overcoming the rejection, which should be removed.

CONCLUSION

In view of the forgoing discussion, it is respectfully submitted that the Examiner's rejections of claims 1-18, 34 and 35 (Groups 1 to 4) are improper and should be reversed by the Board.

Express Mail Label No. EV 699485034 US Date of Deposit: July 6, 2007 I hereby certify that this paper, and the papers and/or fees referred to herein as transmitted, submitted or enclosed, are being deposited with the U.S. Postal Service "Express Mail Post Office to Addressee" on the dated indicated above and is addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450. Name: Laurie A. Drummond Signature: Laurie A. Drummond	Respectfully submitted, **REED SMITH LLP** Tamara J. Yorita Registration No.: 53,813 Maryellen Feehery Hank Registration No.: 44,677 William J. McNichol, Jr. Registration No.: 31,179 2500 One Liberty Place 1650 Market Street Philadelphia, PA 19103-7301 (215) 241-7988 Attorneys for Applicant

IX. Claims Appendix

1. (Previously Amended) A drug delivery system comprising

a pad;

a container; and

a liquid composition, wherein the composition comprises: (1) an effective amount of one or more insoluble dermatologically active ingredients, and (2) an emulsion vehicle for the dermatologically active ingredients,

wherein the composition has a viscosity which is low enough for the composition to substantially uniformly absorb onto the pad via capillary action, and high enough to be substantially retained on the pad, not the container.

2. (Original) The system of claim 1 wherein the viscosity is effective to substantially uniformly deliver the composition to skin when the pad is wiped on the skin.

3. (Original) The system of claim 1 wherein the active ingredient comprises benzoyl peroxide.

4. (Original) The system of claim 3 wherein the benzoyl peroxide comprises particles of less than about 50 microns.

5. (Original) The system of claim 1 wherein the active ingredient comprises particles of about 10 to about 150 microns.

6. (Original) The system of claim 2 wherein the composition is an oil-in-water emulsion.

7. (Original) The system of claim 2 wherein the composition is a water-in-oil emulsion.

8. (Original) The system of claim 2 wherein the composition has a viscosity of about 500 to about 9000 cps measured on a Brookfield viscometer LVT model at about 27°C for 60 seconds and a spindle set for 30 rpm.

9. (Original) The system of claim 2 wherein the composition has a viscosity of about 2000 cps to about 3000 cps measured on a Brookfield viscometer LVT model at about 27°C for 60 seconds and a spindle set for 30 rpm.

10. (Original) The system of claim 2 wherein the composition has a viscosity of about 500 to about 10,000 cps measured on a Brookfield viscometer RVT model with spindle #4 at 20 rpm for 60 seconds at 25°C+-1°C.

11. (Original) The system of claim 2 wherein the composition has a viscosity of about 1900 to about 7,000 cps measured on a Brookfield viscometer RVT model with spindle #4 at 20 rpm for 60 seconds at 25°C+-1°C.

12. (Original) The system of claim 2 wherein the composition has a viscosity of about 4500 to about 6,500 cps measured on a Brookfield viscometer RVT model with spindle #4 at 20 rpm for 60 seconds at 25°C+-1°C.

13. (Original) The system of claim 1 wherein the pad comprises one or more woven materials.

14. (Original) The system of claim 1 wherein the pad comprises one or more non-woven materials.

15. (Original) The system of claim 1 wherein the container comprises a material comprised of metal substantially coated with one or more plastics on at least one surface, and one sheet of the material is heat sealed to a second sheet of the material, and the heat sealed materials contain the pad and the composition without leaking.

16. (Original) The system of claim 1 wherein the active ingredient comprises one or more antifungals.

17. (Original) The system of claim 1 wherein the active ingredient comprises one or more of the group consisting of prodrugs, cosmeceuticals, herbal medicines, traditional medicines, and cutaneously active cosmetic ingredients.

18. (Original) The system of claim 1 further comprising one or more soluble dermatologically active ingredients.

19. (Withdrawn) A drug delivery system comprising

a non-woven pad;

a liquid composition, wherein the composition comprises benzoyl peroxide, starch, carbomer, disodium EDTA, water, glycerin, sodium hydroxide, zinc lactate, glycolic acid, C12-C15 alkyl benzoate, cetearyl alcohol, dimethicone, glyceryl stearate and PEG 100 stearate, steareth 2, steareth 20, and polysorbate 20;

a sealed container, wherein the container comprises a material comprised of metal substantially coated with one or more plastics on at least one surface, and one sheet of the material is heat sealed to a second sheet of the material, and the heat sealed materials contain the pad and the composition without leaking; and

wherein the composition has a viscosity which is low enough for the composition to substantially uniformly absorb onto the pad via capillary action, and high enough to be substantially retained on the pad, not the container.

20. (Canceled)

21. (Withdrawn) The system of claim 19 wherein the viscosity is effective to substantially uniformly deliver the composition to skin when the pad is wiped on the skin.

22. (Withdrawn) The system of claim 19 wherein the benzoyl peroxide comprises particles of less than about 50 microns.

23. (Withdrawn) The system of claim 19 wherein the active ingredient comprises particles of about 10 to about 150 microns.

24. (Withdrawn) The system of claim 19 wherein the composition is an oil-in-water emulsion.

25. (Withdrawn) The system of claim 19 wherein the composition is a water-in-oil emulsion.

26. (Withdrawn) The system of claim 19 wherein the composition has a viscosity of about 500 to about 9000 cps measured on a Brookfield viscometer LVT model at about 27°C for 60 seconds and a spindle set for 30 rpm.

27. (Withdrawn) The system of claim 19 wherein the composition has a viscosity of about 2000 cps to about 3000 cps measured on a Brookfield viscometer LVT model at about 27°C for 60 seconds and a spindle set for 30 rpm.

28. (Withdrawn) The system of claim 19 wherein the composition has a viscosity of about 500 to about 10,000 cps measured on a Brookfield viscometer RVT model with spindle #4 at 20 rpm for 60 seconds at 25°C+-1°C.

29. (Withdrawn) The system of claim 19 wherein the composition has a viscosity of about 1900 to about 7,000 cps measured on a Brookfield viscometer RVT model with spindle #4 at 20 rpm for 60 seconds at 25°C+-1°C.

30. (Withdrawn) The system of claim 19 wherein the composition has a viscosity of about 4500 to about 6,500 cps measured on a Brookfield viscometer RVT model with spindle #4 at 20 rpm for 60 seconds at 25°C+-1°C.

31. (Withdrawn) The system of claim 19 wherein the pad comprises one or more woven materials.

32. (Withdrawn) The system of claim 19 wherein the pad comprises one or more non-woven materials.

33. (Withdrawn) The system of claim 19 wherein the container comprises a material comprised of metal substantially coated with one or more plastics on at least one surface, and one sheet of the material is heat sealed to a second sheet of the material, and the heat sealed materials contain the pad and the composition without leaking.

34. (Previously Presented) The system of claim 1 wherein the active ingredient comprises particles of up to about 300 microns.

35. (Previously Presented) The system of claim 1 wherein the active ingredient comprises particles of less than about 50 microns.

X. Evidence Appendix

Tab 1 World Health Organization website page showing the definition of "traditional medicine" was attached as an exhibit to Applicant's response to the Non-final Office Action and was timely filed and entered on October 4, 2007.

Tab 2 World Health Organization website page showing the definition of "herbal medicines" was attached as an exhibit to Applicant's response to the Non-final Office Action and was timely filed and entered on October 4, 2007.

Tab 3 Presentation slides by Dr. Gerard Bodeker showing examples of "traditional medicines" were attached as an exhibit to Applicant's response to the Non-final Office Action and was timely filed and entered on October 4, 2007.

Tab 4 Definition of "prodrug," was attached as an exhibit to Applicant's response to the Non-final Office Action and was timely filed and entered on October 4, 2007.

Tab 5 Abstracts showing use of the term "prodrug" were attached as an exhibit to Applicant's response to the Non-final Office Action and was timely filed and entered on October 4, 2007.

Tab 6 Definition of "cosmeceutical," was attached as an exhibit to Applicant's response to the Non-final Office Action and was timely filed and entered on October 4, 2007.

Tab 7 U.S. 6,984,391 and U.S. 6,960,300 were attached as an exhibit to Applicant's response to the Non-final Office Action and was timely filed and entered on October 4, 2007.

Tab 8 Examples of insoluble active ingredients from "Martindale: The complete drug reference" were attached as an exhibit to Applicant's response to the Non-final Office Action and was timely filed and entered on October 4, 2007.

Tab 9 U.S. 5,562,642 was entered in the record by the Examiner on June 6, 2005.

Tab 10 U.S. 6,183,766 was entered in the record by the Examiner on June 6, 2005.

Tab 11 U.S. 6,784,145 was entered in the record by the Examiner on June 22, 2006.

Tab 12 U.S. 6,338,855 was entered in the record by the Examiner on June 22, 2006.

XI. Related Proceedings Appendix

None.

WORLD HEALTH ORGANIZATION
Regional Office for the Western Pacific

Traditional medicine

Traditional medicine is an ancient medical practice that existed in human societies before the application of modern science to health. It has evolved to reflect different philosophical backgrounds and cultural origins. Although modern medicine is widely spread, traditional medicine still exists in all countries and areas in the Western Pacific Region. Interest in traditional medicine has increased over the last decade and seems likely to continue. People in many countries are now more prepared to look for alternative approaches to maintain their health. Demands for traditional medicine from the public and the growing economic importance of traditional medicine have led to increased interest on the part of both governments and academic communities in the Region.

Traditional medicine can be defined as the knowledge, skills and practices of holistic health care, recognized and accepted for its role in the maintenance of health and the treatment of diseases. It is based on indigenous theories, beliefs and experiences that are handed down from generation to generation (Development of National Policy on Traditional Medicine, Manila, WHO, 2000).

Fact sheets

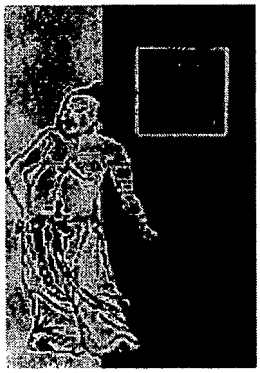
- Traditional Medicine (WHO Headquarters)

News and press releases

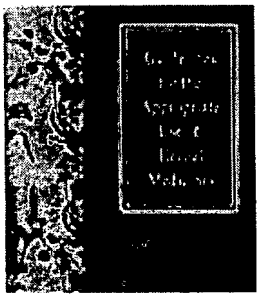
June 2002
Press conference on WHO's traditional medicine strategy
[full text]

12 September 2001
Regional Committee seeks integration of traditional medicine in health services
[full text]

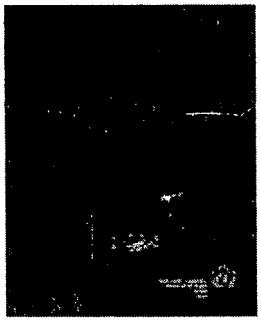
Relevant publications and documents



Guidelines for clinical research in acupuncture
The guidelines aim to encourage the use of systemic laboratory and clinical studies as a way of validating acupuncture, improving its acceptability to modern medicine, and thus extending its use as a simple, inexpensive, and effective therapeutic option. It sets out guidelines that incorporate the established methods and procedures of scientific investigation, yet reflect the special nature of acupuncture as a discipline. The guidelines respond to both growing interest in the therapeutic applications of acupuncture and the need to validate these applications through the compilation of reliable and comparable clinical data.



Guidelines for the appropriate use of herbal medicines
Reports the findings and recommendations of a working group convened to prepare guidelines for the use of herbal medicines in Western Pacific countries. Addressed to national health authorities, the report responds to the widespread use of herbal medicine in this part of the world and the corresponding need for mechanisms to ensure that these products are safe and effective, yet remain broadly accessible. With this need in mind, the report sets out a comprehensive framework for developing national policies designed to control the safety, efficacy, and quality of herbal medicines, manufacturing practices, product registration, and labelling, marketing, and trade.



Regional strategy for traditional medicine in the Western Pacific Region
This strategy was prepared to guide national governments in the Western Pacific Region, WHO and other partners in the efforts to ensure the proper use of traditional medicine and its contribution to maintaining health and fighting diseases in the Region. It has identified strategic directions and actions which provide general principles and guidance for countries and areas to use in responding to the challenges which they may face with consideration of the unique situation in each country and area.

[more publications and documents]

Upcoming meetings and events

No meeting/event planned at this time.

Contacts

trm@wpro.who.int
4th Informal Consultation
on Development of
Standard Acupuncture
Point Locations (video clip)

Focus/Programme

Traditional medicine

Medicines

printable version

Traditional Medicine: Definitions

The following terms are extracted from the General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine.

Click here to view entire document [PDF 216KB]

Traditional medicine

Traditional medicine is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness.

Complementary/alternative medicine (CAM)

The terms "complementary medicine" or "alternative medicine" are used inter-changeably with traditional medicine in some countries. They refer to a broad set of health care practices that are not part of that country's own tradition and are not integrated into the dominant health care system.

Herbal medicines

Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products, that contain as active ingredients parts of plants, or other plant materials, or combinations.

- **Herbs:** crude plant material such as leaves, flowers, fruit, seed, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.
- **Herbal materials:** in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting, or stir-baking with honey, alcoholic beverages or other materials.
- **Herbal preparations:** the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration, or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.
- **Finished herbal products:** herbal preparations made from one or more herbs. If more than one herb is used, the term mixture herbal product can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be herbal.

Traditional use of herbal medicines

Traditional use of herbal medicines refers to the long historical use of these medicines. Their use is well established and widely acknowledged to be safe and effective, and may be accepted by national authorities.

Therapeutic activity

Active ingredients refer to ingredients of herbal medicines with therapeutic activity. In herbal medicines where the active ingredients have been identified, the preparation of these medicines should be standardized to contain a defined amount of the active ingredients, if adequate analytical methods are available. In cases where it is not possible to identify the active ingredients, the whole herbal medicine may be considered as one active ingredient.

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E-mail: trm@who.int

"Indigenous Medical Knowledge: the Law and Politics of Protection"

Dr Gerard Bodeker
Green College
University of Oxford

(The following are overheads presented at the Oxford Intellectual Property Research Centre seminar in St. Peter's College, Oxford on 25th January 2000)

TRADITIONAL HEALTH SYSTEMS

The World Health Organization estimates that the majority of the population of most non-industrial countries still relies on traditional forms of medicine for everyday health care. In many countries up to 80-90% of the population are in this category. Medicinal plants and, to a lesser but important extent, animal products, form the materia medica of these traditions.

Traditional health systems are based in world views or cosmologies that take into account mental, social, spiritual, physical and ecological dimensions of health and well being.

Central importance on the concept of balance - within the individual and between the individual, society and Nature.

Imbalance arises with the breaking of the interconnectedness of life - and results in discomfort and disease.

Traditional health systems have organized frameworks for classifying plants, animals, landscapes and climatic conditions in relation to their effects on health and disease. These taxonomies have much in common with one another and represent a culturally-relevant empirical framework for assessing medicinal plant biodiversity. Such taxonomies may diverge significantly with Western classificatory frameworks and assumptions. This is of importance when determining prior art as it pertains to intellectual property law.

Food and medicine are often viewed interchangeably. Food is medicine. Diet is the basis of health.

Revitalization movements are drawing on traditional medical knowledge to develop integrated modern and traditional health care projects. These movements and other groups have drawn attention to the shrinking availability of medicinal plants to supply the burgeoning need for herbal medicines in non-Western societies and in the industrial countries. Conservation and horticulture programmes are emerging as vital components of the revitalization of local health traditions.

There is a need for coordinated effort by all engaged in medical plant use to generate new policies, mechanisms and resource flows to preserve the biodiversity used in caring for the health of the majority of the world's population.

The Convention on Biological Diversity (CBD)

The CBD is the only major international convention that assigns ownership of biodiversity to indigenous communities and individuals and asserts their right to protect this knowledge.

Article 8 (j): State Parties required to "respect, preserve and maintain knowledge, innovations and practices of indigenous and local communities embodying traditional lifestyles relevant for the conservation and sustainable use of biological diversity and promote the wider application with the approval and involvement of the holders of such knowledge, innovations and practices and encourage the equitable sharing of the benefits arising from the utilisation of such knowledge, innovations and practices."

Article 18.4: Contracting Parties should "encourage and develop models of co-operation for the development and use of technologies, including traditional & indigenous technologies."

The CBD competes for influence with the far more powerful TRIPS.

TRIPS is now the key international agreement promoting the harmonisation of national IPR regimes. Covers **four types** of intellectual property rights:
1. Patents
2. geographical indications
3. undisclosed information (trade secrets)
4. trademarks

- **TRIPS** makes **no reference to the protection of traditional knowledge.** Does not acknowledge or distinguish between indigenous, community-based knowledge and that of industry

- TRIPS does not require adoption of UPOV standards, but rather provision "for the protection of plant varieties either by patents or by an effective *sui generis* system or by any combination thereof." (Art. 27(3)(b)

- The debate over ownership of biodiversity and particularly over medicinal plant and the knowledge associated with it is by no means new.

- In Africa, the 1977 Agreement "Copyright and the Cultural Heritage" far predated any discussions through GATT and subsequently TRIPS on such issues.

- In India a 1988 agreement with the US to establish a plant gene bank caused controversy when India did not secure control over the use of national genetic resources.

- Further more, the issue of harmonising international IP legislation has posed challenges for many countries which have prevented patents on what are deemed to be products essential to the national interest.

- It is against the climate of existing national concern about sovereignty over domestic biological and cultural resources that the debate over TRIPS has occurred.

African Intellectual Property Organization (OAPI), Bangui, March 2, 1977.

Annex VII of the Agreement, "Copyright and the Cultural Heritage," Article 8

"Folklore belongs, in the first instance, to the cultural heritage."

"Folklore" is defined for these purposes to mean "literary, artistic or scientific works as a whole created by the national ethnic communities of the member States, which are passed from generation to generation and which constitute one of the basic elements of the African cultural heritage.

Article 46: "Folklore" includes "scientific knowledge and works: practices and products of medicine and the pharmacopoeia, and theoretical and practical attainments in the fields of the natural sciences."

Article 8(5): Proceeds from royalties deriving from exploitation of these works "shall be used for cultural and social purposes. The conditions under which such royalties are shared shall be fixed in a rule to be promulgated by the competent national authority."

Article 45: In addition to folklore "ethnographic material, such as...products of pharmacopoeia, traditional medicine and psychotherapy" shall be considered "as belonging to the cultural heritage of the nation".

Article 50: It shall be forbidden to unlawfully denature, destroy, export, sell, alienate or transfer, in whole or in part, any of the constituent elements of the cultural heritage.

Article 74: Any person who knowingly violates the provisions of Article 50 is liable to imprisonment of from one month to two years, plus a fine, without prejudice to damages.

However, in the absence of strong national IP legislation and vigorous implementation the existence of such agreements does little to protect countries from exploitation of their medicinal resources and knowledge.

Cameroon is a case in point.

***CAMEROON:** Regulation of bioprospecting is **multisectoral**:*

1. Foreign collectors must obtain a research permit from the Ministry of Scientific and Technical Research (MINRST), before removing samples of resources.

Removal of small quantities of flora, without charge, is authorised.
Permits are negotiated on an individual basis.

No set formula for amount and type of material to be exported for research purposes.

2. Ministry of Environment and Forestry (MINEF), authorised to issue commercial exploitation permits for large-scale extraction of genetic resources for commercial purposes.
MINEF negotiates an export duty with the buyer, using market prices as a guide to set the duty.

- Neither procedure preserves Cameroon's rights to its genetic resources, or ensures return of a fair percentage of the resources' value.

- No mechanism to enforce mandatory value-added processing in-country, nor to negotiate supply contracts, royalties, or ensure sustainable harvesting.

- Forestry Code - potential impact on bioprospecting. **Gives local communities the right to establish community forest reserves with sovereignty over the use of those resources.** Communities could become directly involved in setting terms for access to and use of genetic resources.

- Cameroon intellectual property laws protect patents (including pharmaceutical patents), trademarks, copyright and "cultural patrimony"- including indigenous medical treatments.

- Protection would be limited only to Cameroon.

- New inventions, based on minor variations on traditional knowledge would be eligible for patent protection in industrialised countries.

- Has made no attempt to develop its own capacity to prepare medicinal plant extracts for sale on the world market, nor to link this trade to conservation and local community development.
- Has obtained only a fraction of benefits from medicinal plant trade.

- Example: *prunus africana.* Bark has important anti-cancer properties. Used in treatment of Benign Prostatic Hypertrophy (BPH).

- Being debarked illegally - causes the tree to die, threatening extinction of the species.
- A French company is the sole holder of a commercial exploitation permit to collect and export the bark to the European market.
- The European market was estimated at $150 million in 1992.
- None of the profits are repatriated to Cameroon, whose citizens are paid only for the collection of the bark.

INDIA

- From 1994, Indian Govt did not succeed in repeated attempts to revise 1970 Patent Act to come into line with TRIPS.
- Efforts to do so resulted in riots on streets. Half a million farmers demonstrating.
- Late1999 succeeded in amending it in accord with TRIPS and removing protection for important medicines from patent control.
- Activist groups are now calling for 2005 deadline for coming into line with TRIPS to allow time for full debate and resolution of all of the issues involved.

TURMERIC

- The Centre for Scientific and Industrial Research of India filed a re-examination request with the US Patent and Trademark Office, seeking revocation of a 1994 patent issued to the University of Mississippi.
- Patent, 5,401,504, claimed the use of turmeric for promoting wound healing.
- India argued that turmeric is a well known traditional medicine used in India, and written about by Indian researchers as early as the 1950s.
- India secured a revocation of the patent.
- India is now recording on a set of CD Roms all of the national medicinal plant knowledge. This will be distributed to patent offices world-wide to provide a data base of prior art on Indian traditional medicinal knowledge.
- India is also pursuing a comprehensive legal strategy to seek revocation on non-Indian patents on Indian life forms.

Social & economic costs
of changes in IP legislation

By requiring patents to be applied to pharmaceuticals, it is being argued that TRIPS will have the effect of pricing common drugs out of the reach of most people in poor countries. If herbal medicines are patented - either domestically or internationally - the medicines used as the first and last resort for healthcare by the poor will also become unaffordable. Some examples illustrate the point.

- 200 % increase in cost of medicines after the 1979 introduction of pharmaceutical product patents in **Italy**.

- *Welfare loss* to **Argentina, Brazil, India, Mexico, Korea, and Taiwan**) would amount to a minimum of US$3.5 billion and a maximum of US$10.8 billion. *Income gains* by foreign patent owners would be between US$2.1 billion and US$14.4 billion. (World Bank)

- 'National health disaster' anticipated by the **Indian** Drug Manufacturers' Association from implementation of TRIPs in India.

- 30% of Indian population can afford modern medicines.

- Comparisons of prices of drugs between India and countries where patent protection exists: up to 41 times costlier in countries with patent protection.

- Drug prices in **Malaysia**, where patent protection exists, 20% to 760% higher than in India. Profit-maximising behaviour based on 'what the market can bear'.

SOUTH AFRICA & AIDS DRUGS

- In 1998, President Nelson Mandela signed into a law a measure that would allow South African firms to manufacture low-cost generic versions of the high-price anti-AIDS drugs produced and sold by major Western drug companies.

- Transnational corporations are working to block the law in South African courts. Sought and secured White House support. White House has threatened South Africa with sanctions. V-P Al Gore has pressured South Africa to repeal this law.

- April 30, 1999, the US Trade Representative placed South Africa on its "watch list" for unfair trade practices, citing Pretoria for its attempt to abrogate patent rights.
- Under international trade rules, a country can engage in such "**compulsory licensing**" to combat a national emergency.

- 22.5 million people living with AIDS in sub-Sahara Africa.

- The law also would permit the country to buy drugs when they are found to be cheaper in other nations and import them to South Africa-- **parallel importing.**

- Sept. 1999, **UNAIDS** Exec. Dir. Peter Piot: health care gap between rich and poor countries becoming "morally reprehensible". Called for investigation of "mechanisms such as compulsory licensing, transfer of technology, parallel import of drugs and joint procurement by several countries."

- "Very few Africans - who spend an average of 10 dollars a year on health care - can afford life-prolonging and pain-reducing drugs made in the West, and which cost about 12,000 dollars a year per person." (Plenary presentation to ICASA Conference, Lusaka, Sept. 1999.)

- US manufacturers of AIDS suppressants have blocked Brazil from exporting a product to other countries because of patent rights. Brazil has been able to produce an equivalent of AZT (Zidovudine), which limits mother-to-child transmission, for a 100th of the current costs. **"What is more important patent rights or patients' rights?"** Zimbabwean Health Minister, Dr. T. Stamps. (ICASA Conference, Sept. 9, 1999)

Some IPR Models for the protection of traditional knowledge.

1. **Changing IPR law: Certificates of origin.** (Sociedad Peruana de Derecho Ambiental

Patent applications based on use of genetic resources and/or traditional knowledge should require:

(i) a sworn statement as to the genetic resources and associated knowledge, innovations and practices of indigenous peoples and local communities utilised, directly or indirectly, in the research and development of the subject matter of the IPR application;

(ii) evidence of **prior informed consent** of the country of origin and/or indigenous or local community, as appropriate;

(iii) international standardisation of these conditions through an international certification system.

Countries providing resources and/or traditional knowledge to issue certificates indicating that all obligations to the country and indigenous people/local community had been fulfilled e.g. prior informed consent, equitable benefit sharing, etc. Patent applications would include these certificates. Without them, they would automatically be rejected.

2. Transforming traditional knowledge into trade secrets. (IAD-supported project, Ecuador).

- Knowledge from communities wishing to participate in the project to be catalogued and deposited in a restricted access database. Each community will have its own file in the database.

- Checks will be made to see whether each entry is not already in the public domain and whether other communities have the same knowledge.

- To avoid the danger of a price war from competition among communities, there would be a cartel developed among those communities sharing a trade secret.

- The trade secret can then be negotiated in a Material Transfer Agreement with the benefits shared between the government and the cartel members.

3. Local innovations databases.

Society for Research and Initiatives for Sustainable Technologies and Institutions (SRISTI), India, has developed databases of traditional knowledge and innovations in close collaboration with local community members.

- Advocates a global registration system of local innovations. Individual and collective innovators would receive acknowledgement and financial rewards for commercial applications of their knowledge, innovations and practices.

- Links would be built between small investors, entrepreneurs and innovators for mutual financial benefits.

- Individuals or communities could seek IPR protection in such forms as inventors certificates and petty patents. *(The intellectual property law of Kenya was amended in 1989 to provide for a petty patent for traditional medicinal knowledge.)*

- All national patent offices should be able to access local innovation databases when carrying out prior art searches and examinations.

The World Conservation Union (IUCN) recommends:

- Governments should improve public access to patent databases by such means as publishing patent texts on the Internet
- The development of local knowledge registers that patent examiners could access so as to ensure that traditional knowledge is not pirated. These should be bottom-up participatory programmes.
- Ownership of these registers should not be claimed, since this would be an infringement of the rights of the knowledge providers.
- Recognition and protection by States of the traditional knowledge of these communities, and traditional modes of resource use regulation and dispute resolution under customary law.
- Ensuring the consent and involvement of these communities in the wider use of their knowledge and practices.
- Mandating a series of equitable benefit-sharing measures.
- Exclude plants and animals from patentability until the environmental and social impacts of allowing such patents can be assessed;
- Require more exacting standards of novelty or inventive step so that the failure of IPR law to adequately protect traditional knowledge is not compounded by the ability of others to hold patents for inventions closely derived from such knowledge;
- Apply an interpretation of ***prior art*** that includes public domain knowledge in any part of the world whether published or not.
- Exclude from patentability existing traditional/indigenous knowledge (in current or translated forms), and essentially derived products and processes from such knowledge;
- Develop *sui generis* legislation for protection of folklore based on an understanding of 'folklore' as inclusive of folk knowledge/practices/ expressions of art, craft, music, scientific belief, religious belief, architecture, agriculture, **medicine**, and conservation of natural resources;
- Communities should have the right to define the terms by which they control access and require benefit-sharing – these terms should be transparent.

Examples where controversy has arisen over exploitation and patenting of indigenous medical knowledge.

International Cooperative Biodiversity Groups (ICBG) - Maya.

- **The Contract:** U.S. Government (National Institutes of Health) initiative to identify, patent, and commercialize Mayan knowledge and biological materials - at least in part - through a private biopharmaceutical enterprise.

- University of Georgia (UGA) has been contracted to develop a project relationship with Mexican officials and Mayan communities that will make the extraction and privatization of some of their knowledge/resources mutually acceptable.

- UGA offered the experience and acceptance necessary to obtain the cooperation of Mexican and Mayan authorities.

- **Majority Opposition:** The ICBG in 2nd year - still faces serious local opposition. 24 local organizations in Chiapas have come out in opposition.

- **Minority local support:** According to ICBG-Maya a few local communities appear to have accepted the project. No consensus among the peoples of Chiapas that the project should proceed. Project organizers, say they need more time to convince people. They seem unclear as to when those who are sought for their Prior Informed Consent (PIC) have the right to declare NIC - No Intention of Consenting.

- **'Common' Knowledge:** Who constitutes 'no' or 'yes' ? UGA will begin collecting even if only some of the communities agree.

- **Outside Influences:** Chiapas has sparked the inevitable debate as to whether local communities are being manipulated by outside interests. The ICBG project partners have made this accusation. The Consejo has accused the ICBG project of being dominated by outsiders.

- **RAFI (Rural Advancement Foundation International):** In the absence of effective protocols and regulatory procedures, neither national governments nor intergovernmental treaties can guarantee the integrity of any bioprospecting contract.

- RAFI considers that unless, and until functioning mechanisms are in place, all bioprospecting agreements jeopardize the right and interests of local communities.

- RAFI does not believe that there exists any adequate mechanism including the CBD capable of safeguarding the rights and interests of local communities. RAFI regards all bioprospecting agreements to be biopiracy.

THE KANI & A HERBAL PATENT

Tropical Gardens Botanical Research Institute (TGBRI), Trivandrum, India holds patent on ***Trichopus zeylanicus.*** 'Jeevani' is the local term.

Jeevani's proerties:

- ❖ Immunomodulator
- ❖ Hepato-protective
- ❖ Aphrodisiac

Indigenous knowledge of the plant resides with the Kani tribe in the Western Ghat forests.

TGBRI has commitment to share royalties with the Kani. TGBRI is sole patent holder.

7 year license to Arya Vaidya Pharmacy which produces herbal extracts from Jeevani.

Difficulties:

1. Kani Trust has to negotiate with State Govt for transfer of funds
2. Kerala Forest Dept seeking share of royalites & licence fee.
3. Kani don't hold title to their customary land - Forest Dept. preventing them from harvesting Jeevani.
4. High return on Jeevani plants resulting in over-harvesting by immigrant workers drawn to this source of income.

OTHER HERBAL EXAMPLES

1. Phyllanthus amarus - Ayurvedic treatment for jaundice. U.S. patent for use with Hepatitis B.

2. Piper nigrum. Ayurvedic treatment for vitiligo (a skin pigmentation disorder). UK patent for application of a molecule from piper nigrup for use in treatment of vitiligo.

3. Shaman Pharmaceuticals: AIDS diarrhea herbal drug. Contrct for benefit sharing with source of origin of the information.

FUTURE

1. Debate over patenting will hinge much on what constitutes prior informed consent. How to determine who represents a community, what represents full consent.

2. State vs. Community ownership of indigenous knowledge. Should states get royalties from knowledge that originates from communities within those states. Or should royalties go direct to the traditional knowledge holders?

3. Disputes over patents on herbal products - impact on local herbal use and developing country exports of herbals. (World Bank: $3 trillion herbal market by mid 21st century)

4. More examples of the S. African AIDS drugs type - & with herbals. "Patent rights v. Patients' rights".

5. Restrictions on collaborative research (e.g. India's Biodiversity research approval committee now requires Central Govt approval for all collaborative research pertaining to indigenous knowledge)

6. Southern (Eastern? e.g. ASEAN) alliance to combat prejudicial aspects of TRIPs.

Definition of Prodrug

Prodrug: A precursor (forerunner) of a drug. A prodrug must undergo chemical conversion by metabolic processes before becoming an active pharmacological agent. For example, sulfasalazine is a prodrug. It is not active in its ingested form. It has to be broken down by bacteria in the colon into two products -- 5-aminosalicylic acid (5ASA) and sulfapyridine -- before becoming active as a drug.

Related Articles: From the Doctors at MedicineNet.com

Suggested Reading By Our Doctors:

- bitolterol mesylate, Tornalate - Source:MedicineNet
- famciclovir, Famvir - Source:MedicineNet
- valacyclovir, Valtrex - Source:MedicineNet
- sulfasalazine, Azulfidine - Emphasizes the medication sulfasalazine (Azulfidine), a drug used for the treatment of ulcerative colitis, Crohn's disease, rheumatoid arthritis, or ankylosing spondylitis. Source:MedicineNet

Latest Medical News:

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- Homeopathy: Natural Approach or All a Fake?
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- Nut-Allergic Kids: Nut Mix-up Common
- Warm Watermelon More Nutritious
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1: J Control Release. 2002 Feb 19;79(1-3):113-22.

Percutaneous penetration and skin metabolism of ethylsalicylate-containing agent, TU-2100: in-vitro and in-vivo evaluation in guinea pigs.

Sintov AC, **Behar-Canetti C**, **Friedman Y**, **Tamarkin D**.

Ben Gurion University of the Negev, The Institutes for Applied Research, 84105, Beer Sheva, Israel. asintov@bgumail.bgu.ac.il

The aim of this study was to investigate the percutaneous penetration and dermal metabolism of a new potential anti-acne prodrug--TU-2100 [bis(o-carboxyphenyl ethyl ester)nonanedioate] in guinea pigs. The fluxes of this agent through excised skin after applications of TU-2100 gels at 3 and 10% concentrations were similar. However, after 24 h from the time of drug application, the total amounts of permeated TU-2100 into the skin compartment and through the skin into the receiver were 271.7 (+/-30.7 S.E.) microg/cm(2) from the 3% gel and 779.4.0 (+/-98.5 S.E.) microg/cm(2) from the 10% gel, demonstrating a relatively high skin accumulation. Higher degradation of TU-2100 to ethylsalicylate occurred after application of drug at 10% concentration than after the application of 3% gel. In contrast, the fraction of permeated drug metabolized was twofold higher after the 3% gel application than after the 10% gel (F(m)=20 vs. 10.5 mole %). Since F (m) is reversibly related to the total permeating drug, the obtained values actually reflect the significant difference in TU-2100 permeation from the 3% (271.7 microg) and the 10% (779.4 microg) gels. An in vivo--in vitro comparison revealed similar drug accumulations in the skin after application of both 3 and 10% gels, however, skin metabolism was found to be significantly higher in vivo than in vitro.

PMID: 11853923 [PubMed - indexed for MEDLINE]

1: Br J Dermatol. 2001 May;144(5):983-90.

A quantitative assessment of protoporphyrin IX metabolism and phototoxicity in human skin following dose-controlled delivery of the prodrugs 5-aminolaevulinic acid and 5-aminolaevulinic acid-n-pentylester.

Gerscher S, Connelly JP, Beijersbergen Van Henegouwen GM, MacRobert AJ, Watt P, Rhodes LE.

Dermatology Unit, Department of Medicine, University of Liverpool, Liverpool, U.K.

BACKGROUND: Topical 5-aminolaevulinic acid (ALA) is widely used in photodynamic therapy (PDT) to generate protoporphyrin IX (PpIX) in the skin. However, other prodrugs may be more effective. OBJECTIVES: The pharmacokinetics of ALA- and ALA-n-pentylester-induced PpIX, together with the phototoxicity after PDT, were compared in human skin in vivo, using iontophoresis as a quantitative drug delivery system. METHODS: A series of six increasing doses of equimolar prodrug solutions was iontophoresed into normal skin of the upper inner arms of 20 healthy subjects. The kinetics of PpIX metabolism in skin (n = 4) and the response to light exposure, performed at 4.5 h (n = 6) and 6 h (n = 10) after application, were assessed by skin surface PpIX fluorescence and postirradiation erythema. RESULTS: ALA and ALA-n-pentylester showed a linear correlation between logarithm of dose and PpIX fluorescence ($P < 0.005$), and logarithm of dose and skin phototoxicity with irradiation at 4.5 h ($P < 0.001$ and $P < 0.005$, respectively) and 6 h ($P < 0.05$ and $P < 0.0001$, respectively) after iontophoresis. Higher phototoxicity was observed with ALA-n-pentylester than with ALA when sites were irradiated at 6 h, as indicated by the significantly lower theoretical threshold dose for erythema ($P < 0.05$) and the shift of the PpIX fluorescence/phototoxicity curve towards greater skin erythema at equal PpIX fluorescence levels. Depth of PpIX fluorescence in skin, as determined by fluorescence microscopy, was similar for both prodrugs, but a more homogeneous distribution of PpIX was seen with the more lipophilic ALA-n-pentylester. CONCLUSIONS: The observed greater phototoxicity of ALA-n-pentylester relative to ALA may be attributable to a more favourable PpIX localization in tissue and/or greater intrinsic toxicity.

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Designing for topical delivery: Prodrugs can make the difference

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Keywords

prodrugs • diffusion cell experiments • water solubility • lipid solubility • transformed Potts-Guy equation • series/parallel equation

Abstract

It has been shown for homologous series of prodrugs that those members who were the more water soluble ones gave the greatest enhancement in topical delivery of the parent drug and not the more lipophilic ones. However, until recently models for topical delivery and equations to predict topical delivery focused only on lipid solubility (S_{LIPID}) or partition coefficient ($K_{OCT:AQ}$) and molecular volume (or molecular weight, MW) as parameters. Now several equations (transformed Potts-Guy or Series/Parallel) have been developed which include aqueous solubility (S_{AQ}) as a parameter for predicting flux through skin. Experimental fluxes, solubilities, and MW from seven series of prodrugs have been fit to the transformed Potts-Guy equation to give coefficients for log solubility in isopropyl myristate (log S_{IPM}) and log solubility in water (log S_{AQ}) (0.53 and 0.47, respectively) which show, for parent drugs delivered by prodrugs from IPM *in vitro* through hairless mouse skin, that water solubility is almost as important as lipid solubility. When the transformed Potts-Guy equation was fit to data for the delivery of NSAID from mineral oil (MO) *in vivo* through human skin, the coefficients were 0.72 log S_{MO} and 0.28 log S_{AQ}. When the transformed Potts-Guy equation was fit to data for the delivery of their parent drugs by three series of prodrugs from water *in vitro* through hairless mouse skin the coefficients were 0.66 log S_{IPM} and 0.34 log S_{AQ}. Numerous recent examples are also given where more water-soluble members of homologous series of prodrugs give higher flux values from water vehicles *in vitro* through human skin than the more lipid soluble ones. © 2003 Wiley Periodicals, Inc. Med Res Rev, 23 No. 6, 763-793, 2003

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Definition of Cosmeceutical

Cosmeceutical: A cosmetic product claimed to have medicinal or drug-like benefits. Cosmeceutical products are marketed as cosmetics, but reputedly contain biologically active ingredients. Examples include anti-wrinkle skin creams with ingredients such as alpha lipoic acid and dimethylaminoethanol and creams containing "cellular replenishment serum" that supposedly have "antiaging properties."

The term "cosmeceutical" was created in 1990s from cosm(etic) + (pharma) ceutic. The cosmetic industry uses the term but the US Food and Drug Administration does not recognize the term. While drugs are subject to a review and approval process by FDA, cosmetics are not. If a product has drug properties, it must be approved as a drug. But cosmeceutics skirt this review and approval process.

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COSMECEUTICAL /kɒsmə'juːtɪk(ə)l/

This is a blend of *cosmetic* and *pharmaceutical* which has appeared only in the nineties. It's a well-known term in the pharmaceutical business, which is still most commonly encountered in the USA, but is now increasingly being used elsewhere, and which is moving into more general contexts. It refers to a product which is marketed as a cosmetic, but which contains biologically active ingredients that have an effect on the user. Examples are anti-wrinkle creams, baldness treatments, moisturisers and sunscreens. They are causing problems world-wide for regulatory authorities, such as the American Food and Drugs Administration, which must decide when a product crosses the line between being merely a cosmetic and becoming a drug, the latter having much more stringent controls on its development, testing and supply. Much seems to depend on the labelling of the product: one describing itself as a deodorant would probably be classed as a cosmetic, whereas one labelled as an antiperspirant might well be classified as a drug because it claims to close the pores of the skin.

More prescription drugs are being sold across the counter; some may soon become "cosmeceuticals" or "nutriceuticals"—active chemicals sold as cosmetics or food.

[*Economist*, Apr 1995]

Photodamage, the deterioration of skin due to sun exposure and aging, is the biggest market segment for cosmeceuticals.

[*The Scientist*, Jan 1998]

Martindale

The complete drug reference

Thirty-second edition

Edited by

Kathleen Parfitt

BSc, FRPharmS

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Antifungals

This chapter describes those drugs that are used mainly in the treatment and prophylaxis of fungal infections (mycoses). They include the allylamines (naftifine and terbinafine), several polyene antibiotics (including amphotericin and nystatin), other antifungal antibiotics (for example griseofulvin), azole derivatives, including imidazoles (such as ketoconazole) and triazoles (such as fluconazole and itraconazole), and a number of other compounds among them amorolfine, ciclopirox olamine, flucytosine, haloprogin, tolnaftate, and undecenoic acid and its salts.

Choice of Antifungal

Fungi may be classified as either yeasts or moulds according to their appearance and means of growth. Yeast-like fungi involved in infections include *Candida* spp., *Blastomyces dermatitidis, Coccidioides immitis, Histoplasma capsulatum, Sporothrix schenckii,* and the infective agents of chromoblastomycosis. Examples of pathogenic moulds include *Aspergillus* spp., the dermatophytes, and the Mucorales fungi.

Some fungi are true pathogens and can cause disease in any individual. Other fungi such as *Candida* species and *Pneumocystis carinii* (once thought to be a protozoan but now considered to be a fungus) are of low pathogenicity and require an alteration in the normal defence mechanisms for disease to occur; such disease is called opportunistic.

Fungal infections may be classified as **superficial**, affecting only the skin, hair, nails, or mucous membranes, or **systemic**, affecting the body as a whole; systemic infections tend to occur more frequently in immunocompromised individuals such as those with AIDS. Fungal infections may also be described as **local** when they are restricted to one body area, as **invasive** when there is spread into the tissues, or as **disseminated** when the infection has spread from the primary site to other organs throughout the body.

Ideally antifungal treatment should be chosen after the infecting organism has been identified but it is often necessary to start treatment before the pathogen can be cultured and identified especially in immunocompromised patients in whom infections are rapidly progressive.

The choice of treatment for the important fungal diseases is described below.

Aspergillosis

Aspergillosis is an infection caused by fungi of the genus *Aspergillus*, usually *A. fumigatus* although *A. flavus* and *A. niger* are also important species. Aspergillosis is usually acquired by inhalation and most commonly causes non-invasive disease of the respiratory tract. Other sites of infection include the eye following trauma or cataract surgery. Invasive disease of tissues adjacent to the site of infection, for example spread from the paranasal sinus to the orbit, and dissemination to distant organs may occur, predominantly in immunocompromised patients. In severely immunocompromised patients aspergillosis usually presents as severe acute pneumonia. Other organs affected may include the heart (particularly damaged or prosthetic valves), kidneys, bone, brain, liver, and skin.

In general the response of **invasive** aspergillosis to treatment is poor and early initiation of treatment is essential. Surgical excision may be necessary. High intravenous doses of amphotericin remain the antifungal treatment of choice.[1-3] However, the overall response rate to conventional amphotericin is reported to be only 30 to 35%,[3] although this may be improved by the use of liposomal amphotericin.[4-6] Combination therapy with amphotericin and flucytosine has also been suggested[7] and may be useful in cerebral, meningeal, or endocardial infections.[3] However, itraconazole by mouth[8] is emerging as the main alternative to amphotericin.

A number of approaches to reducing the incidence of aspergillosis in immunocompromised patients have been discussed, including chemoprophylaxis with either low-dose intravenous, intranasal, or nebulised amphotericin, or oral itraconazole[9,10] or a combination of these.[11]

Non-invasive forms of aspergillosis include allergic bronchopulmonary aspergillosis, a hypersensitivity reaction to *Aspergillus* usually occurring in asthmatic patients, and aspergilloma, a fungal mass or ball developing within the pulmonary cavity or paranasal sinus.

Allergic bronchopulmonary aspergillosis is usually treated with corticosteroids although oral itraconazole may be a useful adjunct. The treatment of **aspergilloma** depends on the severity of symptoms, and includes conservative management, antifungal therapy, or surgical resection. Oral itraconazole or intravenous amphotericin are once again the most effective drugs. Direct intracavitary instillation of antifungals has also been advocated for patients at particularly high risk of complications.[12] Inhaled amphotericin aerosol was reported to be poorly tolerated and of little value in preventing invasive pulmonary aspergillosis in granulocytopenic patients.[13]

Chronic locally invasive infections have been reported to respond to prolonged treatment with itraconazole;[14] in this small study, itraconazole produced clinical improvements but not mycological cure.

Aspergillosis of the **eye**, like other fungal eye infections, is difficult to treat; antifungals are generally not well absorbed following topical application and infections extending into the vitreous or anterior chamber require subconjunctival, intra-ocular, and/or systemic treatment. Systemic treatment is necessary for ocular manifestations of disseminated disease. When systemic therapy is required intravenous amphotericin is usually given; an oral azole compound may be given for less severe infections. For superficial eye infections a number of antifungals have been applied topically, including natamycin, amphotericin, azole compounds, and silver sulphadiazine when they have been given alone or as an adjunct to systemic therapy. Surgical excision of infected tissue may be necessary in severe infections.

1. Anonymous. Essential drugs: systemic mycoses. *WHO Drug Inf* 1991; **5**: 129–36.
2. Anonymous. Systemic antifungal drugs. *Med Lett Drugs Ther* 1997; **39**: 86–8.
3. Denning DW. Treatment of invasive aspergillosis. *J Infect* 1994; **28** (suppl 1): 25–33.
4. Ringdén O, *et al.* Efficacy of amphotericin B encapsulated in liposomes (AmBisome) in the treatment of invasive fungal infections in immunocompromised patients. *J Antimicrob Chemother* 1991; **28** (suppl B): 73–82.
5. Chopra R, *et al.* Liposomal amphotericin B (AmBisome) in the treatment of fungal infections in neutropenic patients. *J Antimicrob Chemother* 1991; **28** (suppl B): 93–104.
6. Mills W, *et al.* Liposomal amphotericin B in the treatment of fungal infections in neutropenic patients: a single-centre experience of 133 episodes in 116 patients. *Br J Haematol* 1994; **86**: 754–60.
7. Saral R. Candida and aspergillus infections in immunocompromised patients: an overview. *Rev Infect Dis* 1991; **13**: 487–92.
8. Denning DW, *et al.* NIAID mycoses study group multicenter trial of oral itraconazole therapy for invasive aspergillosis. *Am J Med* 1994; **97**: 135–44. Correction. *ibid.*; 497.
9. Beyer J, *et al.* Strategies in prevention of invasive pulmonary aspergillosis in immunosuppressed or neutropenic patients. *Antimicrob Agents Chemother* 1994; **38**: 911–17.
10. Cafferkey MT. Chemoprophylaxis of invasive pulmonary aspergillosis. *J Antimicrob Chemother* 1994; **33**: 917–24.
11. Todeschini G, *et al.* Oral itraconazole plus nasal amphotericin B for prophylaxis of invasive aspergillosis in patients with hematological malignancies. *Eur J Clin Microbiol Infect Dis* 1993; **12**: 614–18.
12. Kauffman CA. Quandary about treatment of aspergillomas persists. *Lancet* 1996; **347**: 1640.
13. Erjavec Z, *et al.* Tolerance and efficacy of amphotericin B inhalations for prevention of invasive pulmonary aspergillosis in haematological patients. *Eur J Clin Microbiol Infect Dis* 1997; **16**: 364–8.
14. Caras WE, Pluss JL. Chronic necrotizing pulmonary aspergillosis: pathologic outcome after itraconazole therapy. *Mayo Clin Proc* 1996; **71**: 25–30.

Blastomycosis

Blastomycosis (not to be confused with South American blastomycosis, see Paracoccidioidomycosis, below) is an infection caused by the fungus *Blastomyces dermatitidis*. Infection may be through the lungs and is usually followed by dissemination; the skin, skeleton, and genito-urinary system often becoming infected. Blastomycosis has been reported only rarely in patients with AIDS, but when it occurs it may be widely disseminated with CNS involvement and a high mortality.[1]

Intravenous amphotericin, once the mainstay of treatment is reserved for severe cases, CNS disease, cases unresponsive to other treatment, and infections in immunocompromised patients. Mild to moderate disease is treated with an oral azole, usually itraconazole,[2] fluconazole,[3] or ketoconazole. Patients with AIDS may require prolonged suppressive treatment, preferably with an oral azole, after a clinical response has been achieved.[1]

1. Pappas PG, *et al.* Blastomycosis in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1992; **116**: 847–53.
2. Dismukes WE, *et al.* Itraconazole therapy for blastomycosis and histoplasmosis. *Am J Med* 1992; **93**: 489–97.
3. Pappas PG, *et al.* Treatment of blastomycosis with fluconazole: a pilot study. *Clin Infect Dis* 1995; **20**: 267–71.

Candidiasis

Candida spp. are commensal fungi commonly found in the gastro-intestinal tract, mouth, and vagina; they become pathogenic only when natural defence mechanisms fail. *C. albicans* is the species most commonly associated with infection, although infections with other species notably *C. (Torulopsis) glabrata, C. krusei, C. parapsilosis,* and *C. tropicalis* also occur. Predisposing factors for pathogenic *Candida* infection include antibacterial therapy, skin trauma, debility, diabetes mellitus, pregnancy, and immunodeficiency; candidiasis often occurs in patients with HIV infection.

Candidiasis (or candidosis), the general term for pathogenic infection with *Candida*, spp. can be superficial, deep local invasive, or disseminated.

Superficial candidiasis includes infection of the oropharynx, vagina, and skin. Oropharyngeal and vulvovaginal infections are commonly known as thrush. Superficial infections can usually be treated topically with an antifungal although the rare chronic mucocutaneous candidiasis syndrome normally requires systemic treatment. Antifungals used topically include amphotericin, nystatin, terbinafine, and the azole derivatives butoconazole, clotrimazole, econazole, isoconazole, miconazole, terconazole, and tioconazole. The choice of drug is determined by the availability of a suitable formulation for the site of infection as well as by toxicity and duration of treatment.

For **oropharyngeal** infections, agents such as chlorhexidine and povidone-iodine may be useful. Crystal violet has also been used,[1,2] but as well as being cosmet-

and Administration

imazole is an imidazole antifungal used topi- in superficial candidiasis (p.367), and in the infections pityriasis versicolor and dermato- sis (p.371). It may also be used occasionally in eatment of the protozoal infection trichomo- when other drugs are contra-indicated (see

mazole is applied topically two or three times or 2 to 4 weeks as a 1% cream, lotion, or so- in the treatment of fungal skin infections; a wder may be used in conjunction with the or solution and has been applied to prevent re- n. The 1% solution is also used topically for otitis externa. Clotrimazole is given as pessa- dosage regimens of 100 mg for 6 days, for 3 days, or a single dose of 500 mg in the t of vulvovaginal candidiasis; similar doses as a 1, 2, or 10% vaginal cream.

s of clotrimazole 10 mg are dissolved in the treatment or prophylaxis of oral candidia- may be administered five times daily for 14 otrimazole has also been administered by t has now been largely superseded by other gs.

eic dermatitis. Topical preparations containing ole such as clotrimazole, ketoconazole, or micona- ly together with hydrocortisone are used in the nt of seborrhoeic dermatitis (see p.1076).

ell disease. Oral clotrimazole has been in the treatment of sickle-cell disease (p.703).

et al. Therapy with oral clotrimazole induces inhi- the Gardos channel and reduction of erythrocyte de- in patients with sickle cell disease. *J Clin Invest* 1227–34.

ions

rimazole Cream; Clotrimazole Pessaries; imazole and Betamethasone Dipropionate Cream; Cream; Clotrimazole Lotion; Clotrimazole Lozeng- Topical Solution; Clotrimazole Vaginal Tablets.

Preparations (details are given in Part 3)
e: Canesten; Mycofug†; Myko Cordes; Pedikurol; n: Clonea; Gyne-Lotrimin; Hiderm; Lotremin†; *Belg.:* Canestene; Gyno-Canestene; ***Canad.:*** maderm; Myclo-Derm; Myclo-Gyne; Neo-Zol; ***Ger.:*** Antifungol; Antimyk†; Apocanda; Aru C; zoderm Myco; Canesten; Canifug; Clotri OPT; galen; Contrafungin†; cutistad; Dignotrimazol; izid; Gilt; Gyno-Canesten; Holfungin; Imazol; Fungin; Logomed Hautpilz-Salbe; Lokalicid; Mycofug; Mycohaug C; Myko Cordes; Myko- g; Onymyken†; Ovis Neu; Pedisafe; Radikal; mazol†; Uromykol; ***Irl.:*** Canesten; ***Ital.:*** Antimi- Gyno-Canesten; ***Neth.:*** Canesten; ***Norw.:*** Can- ***S.Afr.:*** Canalba; Candaspor; Candizole; Clomaderm; Closcript†; Covospor; Dynaspor; Micomisan; Mycoban; Normospor; Stiema- ***Spain:*** Canesten; Fungidermo; Ictan; Mi- ***Swed.:*** Canesten; Clotriferm†; ***Switz.:*** ne; Clocim; clot-basan†; cutistad; Eurosan; ol; Imazol; ***UK:*** Athletes Foot Cream; Can- ombi; Fungederm; Masnoderm; Mycil Gold; Fungoid; Gyne-Lotrimin; Lotrimin; Lotrimin ycelex-7 Combination Pack; Prescription

Aust.: Myko Cordes; ***Austral.:*** Hydrozole; ***Canad.:*** Lotriderm; ***Ger.:*** Baycuten; Canesten mazol; Imazol comp; Lotricomb; Myko Cordes HC; Lotriderm; ***Ital.:*** Desamix Effe; Meclon; ***Spain:*** Beta Micoter; Clotrasone; ***Switz.:*** Ima- ***UK:*** Canesten HC; Lotriderm; ***USA:*** Lot-

---

Hydrochloride (1983-p)

chloride *(rINNM).*
chloride; 710674-S (croconazole). 1-(1- oxy]phenyl}vinyl)imidazole hydrochlo-

347.2.
(croconazole).

hloride is an imidazole antifungal used nt of superficial cutaneous candidiasis, pityriasis versicolor.
when using an azole antifungal in preg- nts is discussed under Fluconazole,

a preparation no longer actively marketed

Preparations

Proprietary Preparations (details are given in Part 3)
Aust.: Pilzcin; ***Ger.:*** Pilzcin; ***Jpn:*** Pilzcin.

Eberconazole (15271-n)

Eberconazole *(rINN).*
WAS-2160. (±)-1-(2,4-Dichloro-10,11-dihydro-5*H*-diben- zo[*a,d*]cyclohepten-5-yl)imidazole.
$C_{18}H_{14}Cl_2N_2 = 329.2$.
CAS — 128326-82-9.

Eberconazole is an imidazole antifungal under investigation for the topical treatment of superficial fungal skin infections.

Econazole Nitrate (2579-b)

Econazole Nitrate *(BANM, USAN, rINNM).*
C-C2470; Econazoli Nitras; R-14827; SQ-13050. (±)-1-[2,4-Dichloro-β-(4-chlorobenzyloxy)phenethyl]imidazole nitrate.
$C_{18}H_{15}Cl_3N_2O,HNO_3 = 444.7$.
CAS — 27220-47-9 (econazole); 24169-02-6 (econazole nitrate); 68797-31-9 ((±)-econazole nitrate).
Pharmacopoeias. In *Eur.* (see p.viii) and *US.*

A white or almost white, almost odourless, crystalline powder. Very slightly **soluble** in water; soluble in methyl alcohol; slightly soluble in alcohol; sparingly soluble in chloroform and dichloromethane; very slightly soluble to practically insoluble in ether. **Protect** from light.

Adverse Effects and Precautions

Local reactions including burning and irritation may occur when econazole nitrate is applied topically. Contact dermatitis has been reported rarely.

For information about the use of econazole during pregnancy and lactation, see under Pregnancy in Fluconazole, Precautions, p.378.

Porphyria. Econazole nitrate has been associated with clinical exacerbations of porphyria and is considered unsafe in porphyric patients.[1]

1. Moore MR, McColl KEL. *Porphyria: drug lists.* Glasgow: Porphyria Research Unit, University of Glasgow, 1991.

Antimicrobial Action

Econazole is an imidazole antifungal with antimicrobial activity similar to that of ketoconazole (p.383).

Pharmacokinetics

Absorption is not significant when econazole nitrate is applied to the skin or vagina.

Uses and Administration

Econazole is an imidazole antifungal used topically in the treatment of superficial candidiasis (see p.367) and in dermatophytosis and pityriasis versicolor (see Skin Infections, p.371).

Econazole nitrate is applied topically up to 3 times daily as a 1% cream, lotion, powder, or solution in the treatment of fungal skin infections. Treatment is continued for 2 to 4 weeks. It is also used in the treatment of vaginal candidiasis as pessaries of 150 mg once daily at bedtime for 3 consecutive nights; a single dose of 150 mg in a long-acting formulation has also been used. A 1% cream has been used for vulvovaginitis. It may also be applied to the male consort's genital area to prevent re-infection.

Econazole nitrate has also been administered as eye or ear drops.

Bacterial infections. Econazole nitrate 1% applied twice daily was effective in erosive interdigital bacterial infections when compared with placebo.[1]

1. Kates SG, *et al.* The antibacterial efficacy of econazole nitrate in interdigital toe web infections. *J Am Acad Dermatol* 1990; **22:** 583–6.

Preparations

BP 1998: Econazole Cream; Econazole Pessaries.

Proprietary Preparations (details are given in Part 3)
Aust.: Gyno-Pevaryl; Pevalip; Pevaryl; ***Austral.:*** Dermazole; Ecostatin; Pevaryl; ***Belg.:*** Gyno-Pevaryl; Pevaryl; ***Canad.:*** Ecostatin; ***Fr.:*** Dermazol; Furazanol; Gyno-Pevaryl; Pevaryl; ***Ger.:*** Epi-Pevaryl; Epi-Pevaryl Pv; Gyno-Pevaryl; ***Irl.:*** Ecostatin; Gyno-Pevaryl; Pevaryl; ***Ital.:*** Amicel; Biodermin†; Chemionazolo; Dermazol†; Eccelium; Eco Mi; Ecodergin†; Ecorex; Ifenec; Micogin; Micos; Micosten†; Pargin; Pevaryl; Polinazolo; Skilar†; ***Neth.:*** Pevaryl; ***Norw.:*** Pevaryl; ***S.Afr.:*** Gyno-Pevaryl; Pevaryl; ***Spain:*** Ecotam; Etramon; Gyno-Pevaryl; Micoespec; Micoseptil; Pevaryl; ***Swed.:*** Pevaryl; ***Switz.:*** Gyno-Pevaryl; Pevaryl; ***UK:*** Ecostatin; Gyno-Pevaryl; Pevaryl; ***USA:*** Spectazole.

Multi-ingredient: ***Aust.:*** Pevaryl; Pevisone; ***Belg.:*** Pevisone; ***Fr.:*** Pevisone; ***Ger.:*** Epi-Pevaryl Heilpaste; Epipevisone; ***Ital.:*** Pevisone; ***Norw.:*** Pevisone; ***S.Afr.:*** Pevisone; ***Swed.:*** Pevisone; ***Switz.:*** Pevisone; ***UK:*** Econacort; Pevaryl TC.

Enilconazole (12690-t)

Enilconazole *(BAN, USAN, rINN).*
R-23979. (±)-1-(β-Allyloxy-2,4-dichlorophenethyl)imidazole.
$C_{14}H_{14}Cl_2N_2O = 297.2$.
CAS — 35554-44-0.

Enilconazole is an imidazole antifungal used in veterinary medicine as a 0.2% solution for the treatment of fungal skin infections in cattle, horses, and dogs.

Fenticlor (2580-x)

Fenticlor *(BAN, USAN, rINN).*
D-25; HL-1050; NSC-4112; Ph-549; S-7. 2,2'-Thiobis(4-chlorophenol).
$C_{12}H_8Cl_2O_2S = 287.2$.
CAS — 97-24-5.

Fenticlor is an antifungal applied topically in the treatment of dermatophyte infections.

Photosensitivity reactions have been reported.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Spain:* Dermisdin.

Fenticonazole Nitrate (16806-n)

Fenticonazole Nitrate *(BANM, USAN, rINNM).*
Fenticonazoli Nitras; Rec-15/1476. (±)-1-[2,4-Dichloro-β-{[*p*-(phenylthio)benzyl]oxy}phenethyl]imidazole mononitrate.
$C_{24}H_{20}Cl_2N_2OS,HNO_3 = 518.4$.
CAS — 73151-29-8 (fenticonazole nitrate); 72479-26-6 (fenticonazole).
Pharmacopoeias. In *Eur.* (see p.viii).

A white or almost white, crystalline powder. Practically **insoluble** in water; sparingly soluble in dehydrated alcohol; freely soluble in methyl alcohol and in dimethylformamide. **Protect** from light.

Adverse Effects and Precautions

Burning and itching have been reported following the application of fenticonazole nitrate.

The need for caution when using an azole antifungal in pregnant or lactating patients is discussed under Fluconazole, p.378.

References.

1. Pigatto P, *et al.* Evaluation of skin irritation and contact sensitizing potential of fenticonazole. *Arzneimittelforschung* 1990; **40:** 329–31.

Antimicrobial Action

Fenticonazole is an imidazole antifungal active against a range of organisms including dermatophyte pathogens, *Malassezia furfur,* and *Candida albicans.*

References to antibacterial activity.

1. Jones BM, *et al.* Comparison of the in vitro activities of fenticonazole, other imidazoles, metronidazole, and tetracycline against organisms associated with bacterial vaginosis and skin infections. *Antimicrob Agents Chemother* 1989; **33:** 970–2.

Uses and Administration

Fenticonazole nitrate is an imidazole antifungal used topically in the treatment of vulvovaginal candidiasis (p.367). A 200-mg pessary is inserted into the vagina at bedtime for 3 nights or a 600-mg pessary is inserted once only at bedtime. Fenticonazole nitrate is also applied topically for the treatment of fungal skin infections.

Preparations

Proprietary Preparations (details are given in Part 3)
Aust.: Fenizolan; Lomexin; ***Fr.:*** Lomexin; ***Ger.:*** Fenizolan; Lomexin; ***Ital.:*** Falvin; Fentiderm; Fentigyn; Lomexin; ***Switz.:*** Mycodermil; ***UK:*** Lomexin.

ported rarely from combination therapy with flucytosine and amphotericin.

Microbiological interactions. Although flucytosine is generally regarded as having synergistic activity with amphotericin, antagonism of the *in vitro* antifungal activity of *amphotericin* against *Candida* spp. by flucytosine has been reported.[1]

Enhanced antifungal activity against *Cryptococcus neoformans* has been reported using a combination of flucytosine and *fluconazole* in *animal* studies.[2,3]

1. Martin E, *et al.* Antagonistic effects of fluconazole and 5-fluorocytosine on candidacidal action of amphotericin B in human serum. *Antimicrob Agents Chemother* 1994; **38:** 1331–8.
2. Larsen RA, *et al.* Effect of fluconazole on fungicidal activity of flucytosine in murine cryptococcal meningitis. *Antimicrob Agents Chemother* 1996; **40:** 2178–82.
3. Nguyen MH, *et al.* Combination therapy with fluconazole and flucytosine in the murine model of cryptococcal meningitis. *Antimicrob Agents Chemother* 1997; **41:** 1120–3.

Pharmacokinetics

Flucytosine is absorbed rapidly and almost completely from the gastro-intestinal tract. After oral doses of 37.5 mg per kg body-weight every 6 hours, peak plasma concentrations of 70 to 80 μg per mL have been achieved within 2 hours; similar concentrations have been achieved but more rapidly, after an intravenous dose. The plasma-flucytosine concentration for optimum response is 25 to 50 μg per mL. Flucytosine is distributed widely through the body tissues and fluids and diffuses into the CSF; concentrations in the CSF have been reported to be 65 to 90% of those in serum. About 2 to 4% of flucytosine is protein bound.

About 90% of a dose is excreted unchanged by glomerular filtration; a small amount of flucytosine may be metabolised to fluorouracil. The small amount of an oral dose of flucytosine not absorbed from the gastro-intestinal tract is eliminated unchanged in the faeces. The elimination half-life is 2.5 to 6 hours in patients with normal renal function but increases with decreasing renal function. Flucytosine is removed by haemodialysis or peritoneal dialysis.

References.

1. Daneshmend TK, Warnock DW. Clinical pharmacokinetics of systemic antifungal agents. *Clin Pharmacokinet* 1983; **8:** 17–42.
2. Baley JE, *et al.* Pharmacokinetics, outcome of treatment, and toxic effects of amphotericin B and 5-fluorocytosine in neonates. *J Pediatr* 1990; **116:** 791–7.

Uses and Administration

Flucytosine is a fluorinated pyrimidine antifungal used in the treatment of systemic fungal infections. It is mainly used in combination with amphotericin in the treatment of severe systemic candidiasis and cryptococcal meningitis, or with fluconazole in cryptococcal meningitis. It has also been tried in other infections due to susceptible fungi including chromoblastomycosis. The various treatments for the above infections are discussed under Choice of Antifungal, p.367.

Flucytosine is given by *intravenous infusion* as a 1% solution over 20 to 40 minutes. A suggested dose is 200 mg per kg body-weight daily in 4 divided doses; a dose of 100 to 150 mg per kg daily may be sufficient in some patients. Dosage should be adjusted to produce plasma concentrations of 25 to 50 μg per mL. This is particularly important in patients with AIDS who are at increased risk of bone marrow toxicity. Parenteral treatment is rarely given for more than 7 days, except for cryptococcal meningitis when it is continued for at least 4 months.

Because flucytosine is mainly excreted by the kidneys, the dose must be adjusted in patients with renal impairment. One suggested regimen is to give 50 mg per kg every 12 hours to patients with a creatinine clearance of 20 to 40 mL per minute and every 24 hours to patients with a creatinine clearance of 10 to 20 mL per minute. Patients with a creatinine clearance of less than 10 mL per minute may be given a single dose of 50 mg per kg; further doses should be based on plasma concentrations which should not exceed 80 μg per mL.

Flucytosine is given by *mouth* in usual doses of 50 to 150 mg per kg daily in four divided doses. Again, blood concentrations should be monitored and dosage adjusted in patients with renal impairment to avoid accumulation of the drug.

Flucytosine has been used *topically*, but such use may increase problems of resistance.

Administration. Flucytosine has almost always been used in combination with another antifungal, usually amphotericin, since resistance can develop rapidly if it is used alone.[1] Combinations of flucytosine with azole antifungals such as fluconazole have produced encouraging responses in *animal*[2,3] and clinical studies.[4]

1. Viviani MA. Flucytosine—what is its future? *J Antimicrob Chemother* 1995; **35:** 241–4.
2. Larsen RA, *et al.* Effect of fluconazole on fungicidal activity of flucytosine in murine cryptococcal meningitis. *Antimicrob Agents Chemother* 1996; **40:** 2178–82.
3. Nguyen MH, *et al.* Combination therapy with fluconazole and flucytosine in the murine model of cryptococcal meningitis. *Antimicrob Agents Chemother* 1997; **41:** 1120–3.
4. Barbaro G, *et al.* Fluconazole vs itraconazole-flucytosine association in the treatment of esophageal candidiasis in AIDS patients: a double-blind, multicenter placebo-controlled study. *Chest* 1996; **110:** 1507–14.

Preparations

BP 1998: Flucytosine Tablets;
USP 23: Flucytosine Capsules.

Proprietary Preparations (details are given in Part 3)
Aust.: Ancotil; ***Austral.:*** Ancotil†; ***Canad.:*** Ancotil†; ***Fr.:*** Ancotil; ***Ger.:*** Ancotil†; ***Irl.:*** Alcobon; ***Ital.:*** Ancotil; ***Neth.:*** Ancotil; ***Norw.:*** Ancotil; ***S.Afr.:*** Alcobon†; ***Swed.:*** Ancotil; ***Switz.:*** Ancotil; ***UK:*** Alcobon; ***USA:*** Ancobon.

Flutrimazole (10991-c)

Flutrimazole *(BAN, rINN).*

Flutrimazolum; UR-4056. 1-[o-Fluoro-α-(*p*-fluorophenyl)-α-phenylbenzyl]imidazole; (*RS*)-1-(2,4'-Difluorotrityl)imidazole.
$C_{22}H_{16}F_2N_2$ = 346.4.
CAS — 119006-77-8.

Flutrimazole is an imidazole antifungal used topically in the treatment of superficial fungal infections.

The need for caution when using an azole antifungal in pregnant or lactating patients is discussed under Fluconazole, p.378.

References.

1. Alomar A, *et al.* Flutrimazole 1% dermal cream in the treatment of dermatomycoses: a multicentre, double-blind, randomized, comparative clinical trial with bifonazole 1% cream: efficacy of flutrimazole 1% dermal cream in dermatomycoses. *Dermatology* 1995; **190:** 295–300.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Flusporan; Funcenal; Micetal.

Genaconazole (10423-q)

Sch-39304; SM-8668. [*R*-(*R**,*R**)]-α-(2,4-Difluorophenyl)-α[1-(methylsulphonyl)ethyl]-1*H*-1,2,4-triazole-1-ethanol.
$C_{13}H_{15}F_2N_3O_3S$ = 331.3.
CAS — 121650-83-7.

Genaconazole is a triazole antifungal under investigation for systemic use.

Griseofulvin (2561-k)

Griseofulvin *(BAN, rINN).*

Curling Factor; Griseofulvina; Griseofulvinum. (2*S*,4'*R*)-7-Chloro-2',4,6-trimethoxy-4'-methylspiro[benzofuran-2(3*H*),3'-cyclohexene]-3,6'-dione.
$C_{17}H_{17}ClO_6$ = 352.8.
CAS — 126-07-8.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.viii), *Int.*, *Jpn*, *Pol.*, and *US.*

An antifungal substance produced by the growth of certain strains of *Penicillium griseofulvum*, or by any other means. It is a white to creamy- or yellowish-white, odourless or almost odourless powder. The Ph. Eur. specifies that the particles of the powder are generally up to 5 μm in maximum dimension, though larger particles, which may occasionally exceed 30 μm, may be present; USP describes material with a predominance of particles of the order of 4 μm in diameter.

The Ph. Eur. specifies 97 to 102% of $C_{17}H_{17}ClO_6$, calculated on the dried substance; the USP specifies not less than 900 μg of $C_{17}H_{17}ClO_6$ per mg.

Ph. Eur. **solubilities** are: practically insoluble in water; slightly soluble in dehydrated alcohol and in methyl alcohol; freely soluble in dimethylformamide and in tetrachloroethane. USP solubilities are: very slightly soluble in water; sparingly soluble in alcohol; soluble in acetone, chloroform, and dimethylformamide. **Store** in airtight containers.

Adverse Effects

Side-effects are usually mild and transient and consist of headache, skin rashes, dryness of the mouth, an altered sensation of taste, and gastro-intestinal disturbances. Angioedema, erythema multiforme, toxic epidermal necrolysis, proteinuria, leucopenia and other blood dyscrasias, oral candidiasis, peripheral neuropathy, photosensitisation, and severe headache have been reported occasionally. Depression, confusion, dizziness, insomnia, and fatigue have also been reported. Griseofulvin may precipitate or aggravate systemic lupus erythematosus.

There have been a few reports of hepatotoxicity attributed to griseofulvin.

Effects on the skin. A report of fatal toxic epidermal necrolysis in a 19-year-old woman.[1] The reaction was attributed to griseofulvin which she had taken for 6 days; she had also received metronidazole for one day. Erythema multiforme occurred in 3 patients taking griseofulvin for 3 to 10 days.[2]

1. Mion G, *et al.* Fatal toxic epidermal necrolysis after griseofulvin. *Lancet* 1989; **ii:** 1331.
2. Rustin MHA, *et al.* Erythema multiforme due to griseofulvin. *Br J Dermatol* 1989; **120:** 455–8.

Precautions

Griseofulvin is contra-indicated in patients with porphyria, liver failure, or systemic lupus erythematosus.

Griseofulvin is embryotoxic and teratogenic in *rats*. It is contra-indicated in pregnancy. Women should not become pregnant during or within one month of stopping griseofulvin treatment. Since griseofulvin may reduce the effectiveness of oral contraceptives, additional contraceptive precautions should be taken during this time. The manufacturers also warn that men receiving griseofulvin should not father children within six months of treatment. The warning is based on data from *in-vitro* studies using mammalian cells which demonstrated aneuploidy.

Griseofulvin may impair the ability to drive or operate machinery, and has been reported to enhance the effects of alcohol.

Porphyria. Griseofulvin has been associated with acute attacks of porphyria and is considered unsafe in patients with acute porphyria.[1]

1. Moore MR, McColl KEL. *Porphyria: drug lists.* Glasgow: Porphyria Research Unit, University of Glasgow, 1991.

Interactions

Phenobarbitone has been reported to decrease the gastro-intestinal absorption of griseofulvin.

Griseofulvin may increase the rate of metabolism and diminish the effects of some drugs such as coumarin anticoagulants and oral contraceptives. Griseofulvin has also been reported to reduce plasma concentrations of salicylate in a patient taking aspirin (see p.18).

Griseofulvin may enhance the effects of alcohol.

Alcohol. In addition to reports of griseofulvin enhancing the effects of alcohol, a severe disulfiram-like reaction to alcohol has been reported in a patient taking griseofulvin.[1]

1. Fett DL, Vukov LF. An unusual case of severe griseofulvin-alcohol interaction. *Ann Emerg Med* 1994; **24:** 95–7.

Bromocriptine. For a report that griseofulvin can block the response to bromocriptine, see p.1134.

Antimicrobial Action

Griseofulvin is a fungistatic antibiotic which inhibits fungal cell division by disruption of the mitotic spindle structure. It may also interfere with DNA production. It is active against the common dermatophytes, including some species of *Epidermophyton, Microsporum*, or *Trichophyton.*

Propionic Acid (3001-c)

E280; E282 (calcium propionate); E283 (potassium propionate). Propanoic acid.

$C_3H_5CO_2H$ = 74.08.

CAS — 79-09-4.

Pharmacopoeias. In *Fr.* Also in *USNF.*

An oily liquid having a slight pungent, rancid odour. **Miscible** with water, alcohol, and various other organic solvents. **Store** in airtight containers.

Sodium Propionate (3005-x)

E281. Sodium propanoate.

$C_3H_5NaO_2$ = 96.06.

CAS — *137-40-6 (anhydrous sodium propionate); 6700-17-0 (sodium propionate hydrate).*

Pharmacopoeias. In *Fr.* Also in *BP(Vet)* and *USNF.*

Colourless transparent crystals or white granular crystalline powder; odourless or with a slight characteristic odour. Deliquescent in moist air. **Soluble** 1 in 1 of water, 1 in 0.65 of boiling water, and 1 in 24 of alcohol; practically insoluble in chloroform and ether. **Store** in airtight containers.

Propionic acid and its salts are antifungals.

Sodium propionate has been used topically, usually in combination with other antimicrobial agents for the treatment of dermatophyte infections. Eye drops containing sodium propionate have also been used.

Propionic acid and its calcium, sodium, and potassium salts are used in the baking industry as inhibitors of moulds.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Propionat.

Multi-ingredient: *Aust.:* Dermowund; *Austral.:* Mycoderm; Oticane†; *Canad.:* Amino-Cerv; *Fr.:* Angispray; Anti-Rhinyl†; Dermacide; Rhinyl; *Ger.:* Onymyken S†; *Ital.:* Propiazol†; Undetint†; *S.Afr.:* Neopan; *Spain:* Undehache†; *USA:* Amino-Cerv; Prophyllin.

Protiofate (14254-z)

Protiofate *(rINN).*

Dipropyl 3,4-dihydroxy-2,5-thiophenedicarboxylate.

$C_{12}H_{16}O_6S$ = 288.3.

CAS — *58416-00-5.*

Protiofate is a thiophene derivative with antifungal and antiprotozoal activity. It has been used locally in the treatment of vaginal candidiasis and trichomoniasis.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Atrimycon†.

Pyrrolnitrin (3002-k)

Pyrrolnitrin *(USAN, rINN).*

52230; NSC-107654. 3-Chloro-4-(3-chloro-2-nitrophenyl)pyrrole.

$C_{10}H_6Cl_2N_2O_2$ = 257.1.

CAS — *1018-71-9.*

Pyrrolnitrin is an antifungal antibiotic isolated from *Pseudomonas pyrrocinia* and applied topically in the treatment of superficial fungal infections.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Micutrin.

Multi-ingredient: *Ital.:* Micomplex†; Micutrin Beta.

Saperconazole (6498-l)

Saperconazole *(BAN, USAN, rINN).*

R-66905. 2-sec-Butyl-4-[4-(4-{4-[(2*RS*,4*SR*)-2-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethoxy]phenyl}piperazin-1-yl)phenyl]-2,4-dihydro-1,2,4-triazol-3-one.

$C_{35}H_{38}F_2N_8O_4$ = 672.7.

CAS — *110588-57-3.*

Saperconazole is a triazole derivative under investigation for the treatment of systemic fungal infections.

The need for caution when using an azole antifungal in pregnant or lactating patients is discussed under Fluconazole, p.378.

References.

1. Odds FC. Antifungal activity of saperconazole (R66905) in vitro. *J Antimicrob Chemother* 1989; **24:** 533–7.
2. Franco L, *et al.* Saperconazole in the treatment of systemic and subcutaneous mycoses. *Int J Dermatol* 1992; **31:** 725–9.

Sertaconazole Nitrate (17275-r)

Sertaconazole Nitrate *(rINNM).*

Sertaconazoli Nitras. (±)-1-(2,4-Dichloro-β-[(7-chlorobenzo[*b*]thien-3-yl)methoxy]phenethyl)imidazole nitrate.

$C_{20}H_{15}Cl_3N_2OS,HNO_3$ = 500.8.

CAS — *99592-32-2 (sertaconazole); 99592-39-9 (sertaconazole nitrate).*

Pharmacopoeias. In *Eur.* (see p.viii).

A white or almost white powder. Practically **insoluble** in water; sparingly soluble in alcohol and in dichloromethane; soluble in methyl alcohol. **Protect** from light.

Sertaconazole nitrate is an imidazole antifungal used topically in the treatment of superficial candidiasis, dermatophytosis, and pityriasis versicolor.

The need for caution when using an azole antifungal in pregnant or lactating patients is discussed under Fluconazole, p.378.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Zalain; *Spain:* Dermofix; Dermoseptic; Zalain.

Sulbentine (3006-r)

Sulbentine *(rINN).*

Dibenzthion; Sulbentinum. 3,5-Dibenzyltetrahydro-2*H*-1,3,5-thiadiazine-2-thione.

$C_{17}H_{18}N_2S_2$ = 314.5.

CAS — *350-12-9.*

Sulbentine is an antifungal that was applied topically as a nail lacquer in the treatment of fungal nail infections.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Fungiplex†.

Sulconazole Nitrate (16999-m)

Sulconazole Nitrate *(BANM, USAN, rINNM).*

RS-44872; RS-44872-00-10-3. 1-[2,4-Dichloro-β-(4-chlorobenzyl)thiophenethyl]imidazole nitrate.

$C_{18}H_{15}Cl_3N_2S,HNO_3$ = 460.8.

CAS — *61318-90-9 (sulconazole); 61318-91-0 (sulconazole nitrate).*

Pharmacopoeias. In *Fr.* and *US.*

White to almost white crystalline powder. **Soluble** 1 in 3333 of water, 1 in 100 of alcohol, 1 in 130 of acetone, 1 in 333 of chloroform, 1 in 286 of dichloromethane, 1 in 2000 of dioxan, 1 in 71 of methyl alcohol, 1 in 10 of pyridine, and 1 in 2000 of toluene. **Protect** from light.

Adverse Effects and Precautions

Local reactions including burning, itching, and erythema have been reported following sulconazole use.

For information about the use of sulconazole during pregnancy and lactation see under Pregnancy in Fluconazole, Precautions, p.378.

Antimicrobial Action

Sulconazole is an imidazole antifungal with activity against dermatophytes, *Candida* spp., and *Malassezia furfur.*

Uses and Administration

Sulconazole nitrate is an imidazole antifungal applied topically once or twice daily as a 1% cream or solution in the treatment of fungal skin infections including dermatophyte infections and pityriasis versicolor (p.371), and candidiasis (p.367).

Reviews.

1. Benfield P, Clissold SP. Sulconazole: a review of its antimicrobial activity and therapeutic use in superficial dermatomycoses. *Drugs* 1988; **35:** 143–53.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Myk-1; *Fr.:* Myk; *Irl.:* Exelderm; *Ital.:* Exelderm; *Neth.:* Myk-1; *UK:* Exelderm; *USA:* Exelderm.

Terbinafine Hydrochloride (14747-y)

Terbinafine Hydrochloride *(BANM, rINNM).*

SF-86-327 (terbinafine). (*E*)-6,6-Dimethylhept-2-en-4-ynl(methyl)-(1-naphthylmethyl)amine hydrochloride.

$C_{21}H_{26}ClN$ = 327.9.

CAS — *91161-71-6 (terbinafine); 78628-80-5 (terbinafine hydrochloride).*

NOTE. Terbinafine is *USAN.*

Adverse Effects

The most frequent adverse effects following oral administration of terbinafine hydrochloride are gastrointestinal disturbances such as nausea, diarrhoea, anorexia, and mild abdominal pain; headache; and skin reactions including rash or urticaria sometimes with arthralgia or myalgia. Severe skin reactions including cutaneous lupus erythematosus, pustulosis, Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred rarely. Loss or disturbance of taste, photosensitivity, and liver dysfunction with isolated reports of cholestasis, hepatitis, and jaundice, have occurred.

There may be local reactions after topical use of terbinafine.

Postmarketing surveillance of about 10 000 patients[1] suggested the following incidences of adverse effects to oral terbinafine: gastro-intestinal symptoms, 4.7%; dermatological effects, 3.3%; CNS symptoms (commonly headache), 1.8%; taste disturbances, 0.6%; and transient disturbances in liver function, 0.1%. Serious adverse effects possibly or probably related to terbinafine included angioedema, bronchospasm, erythema multiforme, extended stroke, and unilateral leg oedema.

1. O'Sullivan DP, *et al.* Postmarketing surveillance of oral terbinafine in the UK: report of a large cohort study. *Br J Clin Pharmacol* 1996; **42:** 559–65.

Effects on the blood. Neutropenia in one patient and pancytopenia in a second were associated with oral terbinafine and resolved once the drug was withdrawn.[1]

1. Kovacs MJ, *et al.* Neutropenia and pancytopenia associated with oral terbinafine. *J Am Acad Dermatol* 1994; **31:** 806.

Effects on the eyes. The US manufacturer has noted that changes in the lens and retina of the eye have sometimes been associated with oral terbinafine, although the significance of these changes was not known.

Precautions

Terbinafine should be used with caution in patients with impaired hepatic or renal function. It should not be given during breast feeding.

Psoriasis. It has been suggested that terbinafine may provoke or exacerbate psoriasis,[1] and that it should be avoided in patients with this disorder.

1. Wilson NJE, Evans S. Severe pustular psoriasis provoked by oral terbinafine. *Br J Dermatol* 1998; **139:** 168.

Interactions

Plasma concentrations of terbinafine may be increased by drugs that inhibit its metabolism by cytochrome P450, such as *cimetidine*, and decreased by drugs that induce cytochrome P450, such as *rifampicin*. For the effect of terbinafine on *nortriptyline*, see p.277.

Antimicrobial Action

Terbinafine is an allylamine derivative reported to have a broad spectrum of antifungal activity. It is considered to act through inhibition of fungal sterol synthesis. Terbinafine is fungicidal against dermatophytes and some yeasts but only fungistatic against *Candida albicans.*

References.

1. Petranyi G, *et al.* Antifungal activity of the allylamine derivative terbinafine in vitro. *Antimicrob Agents Chemother* 1987; **31:** 1365–8.
2. Schuster I, Ryder NS. Allylamines—mode and selectivity of action compared to azole antifungals and biological fate in mammalian organisms. *J Dermatol Treat* 1990; **1** (suppl 2): 7–9.
3. Clayton YM. Relevance of broad-spectrum and fungicidal activity of antifungals in the treatment of dermatomycoses. *Br J Dermatol* 1994; **130** (suppl 43): 7–8.
4. Leeming JP, *et al.* Susceptibility of Malassezia furfur subgroups to terbinafine. *Br J Dermatol* 1997; **137:** 764–7.

Tolnaftate (3009-n)

Tolnaftate *(BAN, USAN, rINN).*

Sch-10144; Tolnaftatum. *O*-2-Naphthyl *m,N*-dimethylthiocarbanilate.

$C_{19}H_{17}NOS$ = 307.4.

CAS — 2398-96-1.

Pharmacopoeias. In *Eur.* (see p.viii), *Jpn*, and *US.*

A white to creamy-white fine powder, odourless or with a slight odour. Practically **insoluble** in water; slightly or very slightly soluble in alcohol; freely soluble in acetone, in chloroform, and in dichloromethane; sparingly soluble in ether. **Store** in airtight containers. Protect from light.

Adverse Effects

Skin reactions occur rarely with tolnaftate and include irritation and contact dermatitis.

Antimicrobial Action

Tolnaftate inhibits the growth of the dermatophytes *Epidermophyton, Microsporum, Trichophyton* spp., and *Malassezia furfur*, but is not active against *Candida* spp. or bacteria.

Uses and Administration

Tolnaftate is an antifungal used topically as a 1% solution, powder, or cream in the treatment or prophylaxis of superficial dermatophyte infections and of pityriasis versicolor (see p.371). Tolnaftate is applied twice daily for 2 to 6 weeks. Repeat treatment may be required.

Like other topical antifungals, tolnaftate is not considered suitable for deep infections in nail beds or hair follicles but it may be used concomitantly with a systemic drug.

Preparations

USP 23: Tolnaftate Cream; Tolnaftate Gel; Tolnaftate Topical Aerosol Powder; Tolnaftate Topical Powder; Tolnaftate Topical Solution.

Proprietary Preparations (details are given in Part 3)

Aust.: Sorgoran; ***Austral.:*** Antifungal Foot Deodorant; Curatin; Pediderm†; Ringworm Ointment; Tinacare†; Tinacidin†; Tinaderm; Tineafax; ***Canad.:*** Absorbine Antifungal; Pitrex; Scholl Athlete's Foot Preparations; Tinactin; Tritin†; ZeaSorb AF; ***Fr.:*** Pedimycose†; Sporiline; ***Ger.:*** Chlorisept N†; Sorgoa; Tinatox; Tonoftal; ***Irl.:*** Mycil; Tinaderm; ***Ital.:*** Tinaderm; ***S.Afr.:*** Tinaderm; ***Spain:*** Devorfungi; Tinaderm; ***UK:*** Athlete's Foot; Mycil; Tinaderm; Tineafax†; ***USA:*** Absorbine Antifungal†; Aftate; Blis-To-Sol; Breezee Mist Antifungal; Desenex†; Dr Scholl's Athlete's Foot; Dr Scholl's Tritin Antifungal Powder; Genaspor; NP-27†; Quinsana Plus; Tinactin; Ting.

Multi-ingredient: ***Aust.:*** Focusan; ***Austral.:*** Curatin; ***Canad.:*** Absorbine Jr Antifungal; ***Irl.:*** Mycil; Tinaderm-M; ***Neth.:*** Focusan†; ***Norw.:*** Focusan†; ***S.Afr.:*** Duoderm†; Quadriderm; ***Spain:*** Cuatroderm; Wasserderminat; ***Switz.:*** Focusan†; Quadriderm; Undex†; ***UK:*** Mycil; Tinaderm-M; ***USA:*** Absorbine Athletes Foot Care; Dermasept Antifungal; SteriNail.

Triacetin (3010-k)

Triacetin *(rINN).*

Glycerol Triacetate; Glycerolum Triacetas; Glyceryl Triacetate. 1,2,3-Propanetriol triacetate.

$C_9H_{14}O_6$ = 218.2.

CAS — 102-76-1.

Pharmacopoeias. In *Eur.* (see p.viii) and *US.*

A clear, colourless somewhat oily liquid with a slight fatty odour. **Soluble** in water; slightly soluble in carbon disulphide; miscible with alcohol, with chloroform, with dehydrated alcohol, with ether, and with toluene. **Store** in well-filled airtight containers.

Triacetin is reported to possess fungistatic properties based on the liberation of acetic acid. It has been applied topically in the treatment of superficial dermatophyte infections. It has also been used as a plasticiser in oral preparations.

Triacetin may destroy rayon fabric. It should not come into contact with metals.

Undecenoic Acid (3012-t)

Acidum Undecylenicum; 10-Hendecenoic Acid; Undecylenic Acid. Undec-10-enoic acid.

$C_{11}H_{20}O_2$ = 184.3.

CAS — 112-38-9.

Pharmacopoeias. In *Chin., Eur.* (see p.viii), and *US.*

A colourless or pale yellow clear liquid or a white to very pale yellow crystalline mass with a characteristic odour.

Practically **insoluble** in water; freely soluble in, or miscible with, alcohol and ether; freely soluble in fatty and essential oils; miscible with chloroform, and fixed and volatile oils. **Store** in airtight, non-metallic containers at a temperature of 8 to 15°. Protect from light.

Calcium Undecenoate (16172-g)

Calcium Undecylenate *(USAN).* Calcium di(undec-10-enoate).

$(C_{11}H_{19}O_2)_2Ca$ = 406.6.

Pharmacopoeias. In *US.*

A fine white powder with a characteristic odour. Practically **insoluble** in water, in cold alcohol, in acetone, in chloroform, and in ether; slightly soluble in hot alcohol.

Zinc Undecenoate (3014-r)

Undecilinato de Zinco; Zinc Undecylenate; Zinci Undecylenas. Zinc di(undec-10-enoate).

$(C_{11}H_{19}O_2)_2Zn$ = 431.9.

CAS — 557-08-4.

Pharmacopoeias. In *Chin., Eur.* (see p.viii), and *US.*

A fine white or almost white powder. Practically **insoluble** in water, alcohol, and ether. **Protect** from light.

Adverse Effects

Irritation may rarely occur after the topical application of undecenoic acid or its salts.

Antimicrobial Action

Undecenoic acid and its derivatives are active against some pathogenic fungi, including the dermatophytes *Epidermophyton, Trichophyton,* and *Microsporum* spp.

Uses and Administration

Undecenoic acid and its zinc salt are applied topically in the prophylaxis and treatment of superficial dermatophytoses, particularly tinea pedis (p.371). Typical concentrations are undecenoic acid 2 to 5% and zinc undecenoate 20%. They are used in creams, ointments, or powders, often in conjunction with each other. Calcium undecenoate is used as a 10 or 15% powder.

Methyl and propyl undecenoate, sodium sulphosuccinated undecenoic acid monoethanolamide, and undecenoic acid monoethanolamide are used similarly.

Preparations

USP 23: Compound Undecylenic Acid Ointment.

Proprietary Preparations (details are given in Part 3)

Aust.: Mayfung; Pelsano; Umadren; ***Canad.:*** Caldesene; Cruex; ***Fr.:*** Mycodecyl; ***Ger.:*** Benzoderm†; ***Irl.:*** Caldesene; ***Switz.:*** Lubex; Turexan Douche; ***USA:*** Blis-To-Sol; Caldesene; Cruex; Decylenes; Fungoid AF; Protectol.

Multi-ingredient: ***Aust.:*** Crino Cordes; Dequafungan; Mycopol; Mykozem; Pelsano; Salvyl; Tineafax; Umadren; ***Austral.:*** Acnederm; Egomycol; Mycoderm; Pedoz; Sebitar; Seborrol; ***Belg.:*** Pelsano; ***Canad.:*** Athletes Foot Antifungal; Cruex; Desenex; Ovoquinol†; ***Fr.:*** Mycodecyl; Paps; ***Ger.:*** Benzoderm†; Dermaethyl-H†; Dermaethyl†; Fungiderm N†; Gehwol Fungizid; Gehwol Fungizid Creme N; Gehwol Nagelpilz; Kytta-Nagelsalbe†; Mediphon†; Onymyken S†; Psorispray†; Skinman Soft; ***Irl.:*** Ceanel; Desenex; Genisol; Monphytol; Pedamed†; ***Ital.:*** Balta Intimo Soluzione; Genisol; Neo Zeta-Foot; Sideck Shampoo Antiforfora†; Sulfadeck†; Undecilenderminat; Undetin†; Zeta-Foot†; ***S.Afr.:*** AF; Ceanel; Mycota; Pedil; ***Spain:*** Acnosan; Infalinat; Pentoderm†; ***Switz.:*** Crimanex; Fungex; Pelsano; Pruri-med; Sebo Shampooing; Trosyd†; Turexan Creme; Turexan Emulsion; Undex†; ***UK:*** Ceanel; Genisol†; Healthy Feet; Monphytol; Mycota; Phytocil†; ***USA:*** Dermasept Antifungal; Desenex; Gordochom; Pedi-Pro; Phicon-F; SteriNail.

Voriconazole (18393-l)

Voriconazole *(BAN, rINN).*

UK-109496; Voriconazol. (2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1,2,4-triazol-1-yl)butan-2-ol.

$C_{16}H_{14}N_5F_3O$ = 349.3.

CAS — 137234-62-9.

Voriconazole is a triazole antifungal under investigation for systemic use.

References.

1. Radford SA, *et al.* In vitro studies of activity of voriconazole (UK-109,496), a new triazole antifungal agent, against emerging and less-common mold pathogens. *Antimicrob Agents Chemother* 1997; **41:** 841–3.
2. Ruhnke M, *et al.* In vitro activities of voriconazole (UK-109,496) against fluconazole-susceptible and -resistant Candida albicans isolates from oral cavities of patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1997; **41:** 575–7.
3. McGinnis MR, *et al.* In vitro evaluation of voriconazole against some clinically important fungi. *Antimicrob Agents Chemother* 1997; **41:** 1832–4.
4. Schwartz S, *et al.* Successful treatment of cerebral aspergillosis with a novel triazole (voriconazole) in a patient with acute leukaemia. *Br J Haematol* 1997; **97:** 663–5.

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3. Pierard-Franchimont C, *et al.* Topical benzoyl peroxide increases the sebum excretion rate. *Br J Dermatol* 1984; **110:** 506.
4. Bojar RA, *et al.* The short-term treatment of acne vulgaris with benzoyl peroxide: effects on the surface and follicular cutaneous microflora. *Br J Dermatol* 1995; **132:** 204–8.
5. Eady EA, *et al.* Effects of benzoyl peroxide and erythromycin alone and in combination against antibiotic-sensitive and -resistant skin bacteria from acne patients. *Br J Dermatol* 1994; **131:** 331–6.
6. Eady EA, *et al.* The effects of acne treatment with a combination of benzoyl peroxide and erythromycin on skin carriage of erythromycin-resistant propionibacteria. *Br J Dermatol* 1996; **134:** 107–13.

Preparations

BP 1998: Benzoyl Peroxide Cream; Benzoyl Peroxide Gel; Benzoyl Peroxide Lotion; Potassium Hydroxyquinoline Sulphate and Benzoyl Peroxide Cream;
USP 23: Benzoyl Peroxide Gel; Benzoyl Peroxide Lotion; Erythromycin and Benzoyl Peroxide Topical Gel.

Proprietary Preparations (details are given in Part 3)
Aust.: Akneroxid; Benzaknen; PanOxyl; Scherogel; Ultra-Clear-A-Med; *Austral.:* Acnacyl†; Benzac; Brevoxyl; Clearasil Ultra Medication; Neutrogena Acne Mask; Oxy; PanOxyl; Skitz†; Topex†; *Belg.:* Akneroxid; Benzac; Pangel; Scherogel; Tinagel; *Canad.:* Acetoxyl; Acnomel BP 5; Benoxyl; Benzac; Benzagel; Clearasil B.P. Plus; Dermacne; Dermoxyl; Desquam-X; H_2Oxyl; Loroxide; Neutrogena Acne Mask; Neutrogena On-The-Spot Acne Lotion; Oxy; Oxyderm; PanOxyl; Solugel; *Fr.:* Cutacnyl; Eclaran; Effacne; Pannogel; PanOxyl; *Ger.:* Akne-Aid-Lotion mild†; Aknederm Oxid; Aknefug-oxid†; Akneroxid; Benzaknen; Benzoyt; Cordes BPO; H_2 Oxyl†; Klinoxid; Logomed Akne-Gel†; Marduk; Oxy Fissan; PanOxyl; Sanoxit; Scherogel; *Irl.:* Acnecide; Benoxyl; PanOxyl; *Ital.:* Benoxid; Benzac; Benzomix; Clearasil Ultra; Delta 80; PanOxyl; Reloxyl; Samil-O_2†; Scherogel; *Neth.:* Akneroxid; Benzac; Peauline†; Tinagel†; *Norw.:* Basiron; PanOxyl; *S.Afr.:* Benoxyl; Benzac-AC; PanOxyl; *Spain:* Acne-Aid†; Aldoacne; Benoxygel; Clearamed; Oxiderma; Oxytokot†; PanOxyl; Peroxacne; Peroxiben; Scherogel†; Stop Espinilla Normaderm; *Swed.:* Basiron; Clearamed†; Mytolac†; Stioxyl; *Switz.:* Acnefuge; Akneroxid; Aknex; Basiron; Benzac; Desanden; Effacne; H_2Oxyl†; Ledoxid Acne; Lubexyl; PanOxyl; *UK:* Acetoxyl†; Acnecide; Acnegel†; Benoxyl; Benzagel†; Clearasil Max 10; Mediclear; Nericur; Oxy; PanOxyl; Ultra Clearasil†; Valderma Active†; *USA:* Ambi 10; Ben-Aqua; Benoxyl; Benzac; Benzagel; Benzashave; Blemerase; Brevoxyl; Buf-Oxal†; Clear By Design; Clearasil; Cuticura†; Del Aqua; Dermoxyl†; Desquam; Exact; Fostex; Loroxide; Neutrogena Acne Mask; Oxy; PanOxyl; Peroxin; Persa-Gel; Theroxide†; Triaz; Vanoxide; Xerac BP†.

Multi-ingredient: *Austral.:* Clearasil Extra Strength†; *Belg.:* Acnidazil; Benzamycin; *Canad.:* Persol; Sulfoxyl; Vanoxide-HC†; *Fr.:* Uvacnyl†; *Ger.:* Acnidazil; *Irl.:* Benzamycin; Quinoderm; *Ital.:* Acnidazil; Delta 80 Plus; Katoxyn; *Neth.:* Acnecure; Acnidazil; *S.Afr.:* Acneclear; Acnidazil; Benzamycine; Quinoderm-H; Quinoderm†; *Switz.:* Acne Creme Plus; Acnidazil; Quinoderm; Quinoderm Hydrocortisone†; *UK:* Acnidazil; Benzamycin; Quinoderm; Quinoderm with Hydrocortisone†; Quinoped; *USA:* Benzamycin; Sulfoxyl; Vanoxide-HC.

Calamine (1598-f)

Prepared Calamine.

Pharmacopoeias. In *Br., Chin., Int.,* and *US.*

The BP describes calamine as a basic zinc carbonate coloured with ferric oxide whereas the USP describes as zinc oxide with a small proportion of ferric oxide.

Calamine is an amorphous, impalpable, pink or reddish-brown powder, the colour depending on the variety and amount of ferric oxide present and the process by which it is incorporated. Practically **insoluble** in water; it dissolves with effervescence in hydrochloric acid.

Calamine has mild astringent and antipruritic actions and is used as a dusting-powder, cream, lotion, or ointment in a variety of skin conditions.

Preparations

BP 1998: Aqueous Calamine Cream; Calamine and Coal Tar Ointment *(Compound Calamine Ointment)*; Calamine Lotion; Calamine Ointment;
USP 23: Calamine Lotion; Phenolated Calamine Lotion.

Proprietary Preparations (details are given in Part 3)
USA: Calamox.

Multi-ingredient: *Austral.:* Animine; Ansenet†; Bronzt; Calaband; Caladryl; Calistaflex†; Dermalife Plus; Quinaband; Septacenet†; Ungvita; *Canad.:* Aveeno Anti-Itch; Caladryl; Calamine Antihistamine; Calmasol†; Ivarest†; Noivy; *Irl.:* Caladryl; Hydrocal; RBC; Vasogen; *Neth.:* Caladryl; *S.Afr.:* Beracal†; Biohist; Caladryl; Calasthetic; Histamed; Lacto Calamine; Pasta Prurat†; *Spain:* Caladryl; Poliglicol Anti Acne; Talco Antihistam Calber; Talquissar; Talquistina; *UK:* Cal-A-Cool†; Calaband; Caladryl; Eczederm†; Hydrocal†; Lacto Calamine; Quinaband; RBC; Swarm; Vasogen; *USA:* Aveeno Anti-Itch; Caladryl; Calamatum; Calamycin; Dome-Paste; Ivarest; RA Lotion; Resinol; Rhuli Spray.

Calcipotriol (10943-p)

Calcipotriol *(BAN, rINN).*
Calcipotriene *(USAN);* MC-903. (5*Z*,7*E*,22*E*,24*S*)-24-Cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol.
$C_{27}H_{40}O_3$ = 412.6.
CAS — 112828-00-9; 112965-21-6.

Adverse Effects and Precautions

The most frequent adverse effect associated with calcipotriol is skin irritation and it should not therefore be applied to the facial area. Symptoms may include burning, itching, erythema, and dry skin, but discontinuation of therapy is seldom necessary. Aggravation of psoriasis may occur. Hypercalcaemia that is rapidly reversible on withdrawal has occurred during treatment with calcipotriol and it should not be used in patients with disorders of calcium metabolism. Other adverse effects include skin atrophy and photosensitivity.

Effects on calcium homoeostasis. Calcipotriol is a vitamin D derivative and therefore has the potential to cause hypercalcaemia and hypercalciuria. Up to December 1993, when about 150 000 patients in the UK had been treated with calcipotriol, the UK Committee on Safety of Medicines had received 6 reports of hypercalcaemia and 2 of hypercalciuria.[1] Three of the patients with hypercalcaemia either had used doses in excess of the recommended maximum (see Uses and Administration, below) or had pustular or exfoliative psoriasis. Hypercalcaemia and hypercalciuria were reversible on withdrawal of calcipotriol. A study[2] investigating the effect of calcipotriol on urine calcium excretion found that use of the maximum recommended dose for four weeks produced increased urine calcium excretion, and the authors suggested that patients requiring the maximum dose of calcipotriol should be monitored for hypercalciuria before and during treatment. A review[3] of the effects of vitamin D analogues on calcium homoeostasis concluded that patients with unstable psoriasis are at particular risk of toxicity from calcipotriol and that measurement of urine calcium excretion is a more sensitive indicator of toxicity than serum-calcium concentrations.

1. Committee on Safety of Medicines/Medicines Control Agency. Dovonex ointment (calcipotriol). *Current Problems* 1994; **20:** 3.
2. Berth-Jones J, *et al.* Urine calcium excretion during treatment of psoriasis with topical calcipotriol. *Br J Dermatol* 1993; **129:** 411–14.
3. Bourke JF, *et al.* Vitamin D analogues in psoriasis: effects on systemic calcium homeostasis. *Br J Dermatol* 1996; **135:** 347–54.

Uses and Administration

Calcipotriol is a vitamin D_3 derivative. *In vitro* it appears to induce differentiation and to suppress proliferation of keratinocytes.

Calcipotriol is used in a cream or ointment for the management of mild to moderate plaque psoriasis and as a solution in the management of scalp psoriasis; the concentration of calcipotriol used is 0.005%. In adults, applications should be made once or twice daily. No more than 100 g of cream or ointment and no more than 60 mL of scalp solution should be applied in one week. If used in combination the limit is 60 g of cream or ointment together with 30 mL of scalp solution or 30 g of cream or ointment with 60 mL of scalp solution.

In children, the cream or ointment may be applied twice daily. No more than 50 g of cream or ointment should be applied in one week in children aged 6 to 12 years; not more than 75 g per week should be applied in children over 12-years-old.

Skin disorders. Topical drugs are the treatment of first choice for chronic plaque psoriasis (p.1075). Calcipotriol, dithranol, and coal tar are commonly used for mild to moderate forms of the disorder. Calcipotriol has been shown to be effective[1] and has the advantages of being odourless and non-staining. Its efficacy in children[2] and during long-term[3] use has also been demonstrated. A study comparing calcipotriol ointment with coal tar for chronic plaque psoriasis[4] found rapid improvement within the first 2 weeks of treatment with calcipotriol, whereas improvement with tar occurred only after 4 weeks. When solutions of calcipotriol and betamethasone were compared for mild to moderate scalp psoriasis,[5] calcipotriol produced a satisfactory response, but betamethasone was more effective and was associated with less irritation of the scalp and face. Combination of calcipotriol with other antipsoriatic drugs may be beneficial; combination with betamethasone was more effective than treatment with calcipotriol alone in one study[6] and in another,[7] addition of calcipotriol to treatment with acitretin improved efficacy.

Beneficial results with calcipotriol have also been reported in pityriasis rubra pilaris[8] and congenital ichthyoses.[9]

1. Murdoch D, Clissold SP. Calcipotriol: a review of its pharmacological properties and therapeutic use in psoriasis vulgaris. *Drugs* 1992; **43:** 415–29.
2. Darley CR, *et al.* Safety and efficacy of calcipotriol ointment (Dovonex®) in treating children with psoriasis vulgaris. *Br J Dermatol* 1996; **135:** 390–3.
3. Ellis JP, *et al.* Long-term treatment of chronic plaque psoriasis with calcipotriol ointment in patients unresponsive to short-contact dithranol. *Eur J Clin Res* 1995; **7:** 247–57.
4. Tham SN, *et al.* A comparative study of calcipotriol ointment and tar in chronic plaque psoriasis. *Br J Dermatol* 1994; **131:** 673–7.
5. Klaber MR, *et al.* Comparative effects of calcipotriol solution (50 μg/mL) and betamethasone 17-valerate solution (1 mg/mL) in the treatment of scalp psoriasis. *Br J Dermatol* 1994; **131:** 678–83.
6. Ruzicka T, Lorenz B. Comparison of calcipotriol monotherapy and a combination of calcipotriol and betamethasone valerate after 2 weeks' treatment with calcipotriol in the topical therapy of psoriasis vulgaris: a multicentre, double-blind, randomized study. *Br J Dermatol* 1998; **138:** 254–8.
7. van de Kerkhof PCM, *et al.* The effect of addition of calcipotriol ointment (50 μg/g) to acitretin therapy in psoriasis. *Br J Dermatol* 1998; **138:** 84–9.
8. van de Kerkhof PCM, Steijlen PM. Topical treatment of pityriasis rubra pilaris with calcipotriol. *Br J Dermatol* 1994; **130:** 675–8.
9. Lucker GPH, *et al.* Effect of topical calcipotriol on congenital ichthyoses. *Br J Dermatol* 1994; **131:** 546–50.

Preparations

Proprietary Preparations (details are given in Part 3)
Aust.: Psorcutan; *Austral.:* Daivonex; *Belg.:* Daivonex; *Canad.:* Dovonex; *Fr.:* Daivonex; *Ger.:* Daivonex; Psorcutan; *Irl.:* Dovonex; *Ital.:* Daivonex; Psorcutan; *Neth.:* Daivonex; *Norw.:* Daivonex; *S.Afr.:* Dovonex; *Spain:* Daivonex; *Swed.:* Daivonex; *Switz.:* Daivonex; *UK:* Dovonex; *USA:* Dovonex.

Centella (1600-d)

Herba Centellae; Hydrocotyle; Indian Pennywort.
CAS — 18449-41-7 (madecassic acid); 464-92-6 (asiatic acid); 16830-15-2 (asiaticoside).
Pharmacopoeias. In *Chin.*

The fresh and dried leaves and stems of *Centella asiatica* (=*Hydrocotyle asiatica*) (Umbelliferae). It contains madecassic acid, asiatic acid, and asiaticoside.

Centella has been used topically and by mouth in the management of wounds, ulcers, and keloid scars. Contact dermatitis has been reported.

The names gotu kola, gotu cola, and gota kola are used for *Centella asiatica* in herbal medicine. Centella is also used in homoeopathic medicine.

References.

1. Santucci B, *et al.* Contact dermatitis due to Centelase®. *Contact Dermatitis* 1985; **12:** 39.

Preparations

Proprietary Preparations (details are given in Part 3)
Aust.: Collaven; Madecassol; *Belg.:* Madecassol; *Canad.:* Cothlyne; Madecassol†; *Fr.:* Madecassol; Madecassol Tulgras; Madecassol†; *Ital.:* Centellase; *Neth.:* Madecassol†; *Spain:* Blastoestimulina; *Switz.:* Madecassol.

Multi-ingredient: *Austral.:* Zestabs†; *Fr.:* Madecassol Neomycine Hydrocortisone; *Ger.:* Emdecassol†; *Ital.:* Angioton; Fluiven; Neomyrt Plus; *Spain:* Blastoestimulina.

Cerous Nitrate (12550-q)

Cerium Nitrate.
$Ce(NO_3)_3$ = 326.1.
CAS — 10108-73-3.

Cerous nitrate has been used topically in conjunction with silver sulphadiazine in the treatment of burns.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Belg.:* Flammacerium; *Fr.:* Flammacerium; *Neth.:* Flammacerium.

Crilanomer (2788-y)

Crilanomer *(rINN).*
Acrylonitrile-starch Copolymer; ZK-94006. A starch polymer with acrylonitrile.
CAS — 37291-07-9.

Crilanomer is a starch copolymer used as a hydrogel wound dressing in the management of wounds.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Intrasite; *Fr.:* Intrasite; *S.Afr.:* Intrasite.

Dithranol (1606-g)

Dithranol (*BAN, rINN*).

Anthralin; Dioxyanthranol; Dithranolum. 1,8-Dihydroxyanthrone; 1,8-Dihydroxy-9(10*H*)-anthracenone.

$C_{14}H_{10}O_3$ = 226.2.

CAS — 1143-38-0 (dithranol); 16203-97-7 (dithranol triacetate).

Pharmacopoeias. In *Chin., Eur.* (see p.viii), and *US.*

A yellow to yellowish-brown, odourless, crystalline powder. Practically **insoluble** in water; slightly soluble in alcohol, in ether, and in glacial acetic acid; soluble in chloroform and in dichloromethane; soluble to sparingly soluble in acetone; dissolves in dilute solutions of alkali hydroxides. The filtrate from a suspension in water is neutral to litmus. **Store** at a temperature of 8° to 15° in airtight containers. Protect from light.

CAUTION. *Dithranol is a powerful irritant and should be kept away from the eyes and tender parts of the skin.*

Stability. The stability of dithranol has been studied in a number of bases and vehicles.[1,2] The weaker preparations of dithranol may be the least stable.[1] Salicylic acid is included in dithranol preparations as an antoxidant and its inclusion in pastes also containing zinc oxide prevents their discoloration due to the inactivation of dithranol by zinc oxide.[3] However, zinc oxide or starch can be omitted from dithranol pastes without loss of effectiveness provided stiffness is maintained.[3] Addition of ascorbic or oxalic acid may improve dithranol's stability in 'Unguentum Merck' but salicylic acid appears to be ineffective.[1] The effect of salicylic acid on the instability of dithranol in yellow soft paraffin is variable[1,2] and its inclusion has been questioned as it can be irritant and percutaneous absorption can be significant.[1] Dithranol is relatively stable in white soft paraffin.[1]

The application of any type of heat and contact with metal spatulas should be avoided during the manufacture of dithranol pastes[4] and if milling facilities are not available dithranol can be incorporated into Lassar's paste by dissolving it first in chloroform.[3]

1. Green PG, *et al.* The stability of dithranol in various bases. *Br J Dermatol* 1985; **113** (suppl 29): 26.
2. Lee RLH. Stability of dithranol (anthralin) in various vehicles. *Aust J Hosp Pharm* 1987; **17**: 254–8.
3. Comaish S, *et al.* Factors affecting the clearance of psoriasis with dithranol (anthralin). *Br J Dermatol* 1971; **84**: 282–9.
4. *PSGB Lab Report P/79/1* 1979.

Adverse Effects and Precautions

Dithranol may cause a burning sensation especially on perilesional skin. Patients with fair skin may be more sensitive than those with dark skin. It is irritant to the eyes and mucous membranes. Use on the face, skin flexures, and genitals should be avoided. Hands should be washed after use.

Dithranol should not be used for acute or pustular psoriasis or on inflamed skin. It stains skin, hair, some fabrics, plastics, and enamel. Staining of bathroom ware may be less of a problem with creams than ointments. Stains on skin and hair disappear on cessation of treatment although such disappearance may be slow.

Uses and Administration

Dithranol is used in the treatment of subacute and chronic psoriasis usually in one of two ways. *Conventional treatment* is commonly started with an ointment or paste containing 0.1% dithranol (0.05% in very fair patients) applied for a few hours; the strength is gradually increased as necessary to 0.5%, occasionally to 1%, and the duration of contact extended to overnight periods or longer. The preparation is sparingly and accurately applied to the lesions only. If, on initial treatment, lesions spread or excessive irritation occurs, the concentration of dithranol or the frequency of application should be reduced; if necessary, treatment should be stopped. After each treatment period the patient should bathe or shower to remove any residual dithranol.

For *short-contact therapy* dithranol is usually applied in a soft basis to the lesions for up to 60 minutes daily, before being washed off. As with conventional treatment the strength used is gradually increased from 0.1% to 2% but strengths up to 5% have been used. Surrounding unaffected skin may be protected by white soft paraffin.

Treatment for psoriasis should be continued until the skin is entirely clear. Intermittent courses may be needed to maintain the response. Treatment schedules often involve coal tar and UV irradiation (preferably UVB) before the application of dithranol (see below). Salicylic acid is included in many topical preparations of dithranol.

A cream containing dithranol triacetate 1% has been used similarly to dithranol in conventional treatment of psoriasis.

Psoriasis. Dithranol used alone or with coal tar with or without ultraviolet light continues to be one of the drugs of first-line treatment for psoriasis (p.1075). It is particularly suited to the treatment of stable chronic plaque psoriasis but unlike coal tar, is irritant to healthy skin and care is required to ensure that it is only applied to lesions. Treatment with dithranol is therefore more feasible when the plaques are large or few in number. Concomitant use of coal tar may help to reduce the irritant effects of dithranol without affecting efficacy. Traditional treatment with dithranol is time consuming and more suitable for use on hospital inpatients. Dithranol formulated in stiff preparations such as Lassar's paste to minimise spreading to perilesional skin is left on overnight covered with a suitable dressing and washed off the next day. Treatment is usually initiated with a concentration of 0.1% (0.05% in fair-skinned patients) and gradually increased according to the response and irritation produced. Cream formulations may be less effective but are more suitable for domestic use. Dithranol is also used with UVB phototherapy and there have been many modifications of the original Ingram's regimen in which dithranol is applied after bathing in a tar bath and exposure to ultraviolet light. Inpatient stays of up to 3 weeks may be required but long periods of remission can be obtained. However, short-contact therapy in which concentrations of up to 5% of dithranol are applied daily for up to 1 hour are more suitable for use on an outpatient basis and there appears to be little reduction in efficacy; irritation and staining may also be reduced.

Preparations

BP 1998: Dithranol Cream; Dithranol Ointment; Dithranol Paste; ***USP 23:*** Anthralin Cream; Anthralin Ointment.

Proprietary Preparations (details are given in Part 3)
Austral.: Dithrocream; ***Canad.:*** Anthraforte; Anthranol; Anthrascalp; ***Fr.:*** Anthranol†; Dithrasist†; ***Irl.:*** Dithrocream; Micanol; ***Ital.:*** Psoridern; ***Neth.:*** Psoricreme; ***Norw.:*** Micanol; ***S.Afr.:*** Anthranol†; ***Spain:*** Anthranol; ***Swed.:*** Amitase†; Micanol; ***UK:*** Alphodith†; Anthranol†; Dithrocream; Exolan†; Micanol; ***USA:*** Anthra-Derm; Dritho-Scalp; Drithocreme; Micanol; Miconal.

Multi-ingredient: ***Aust.:*** Anthraderm; Psoradexan; ***Austral.:*** Dithrasal; Psorin†; ***Fr.:*** Anaxeryl; ***Ger.:*** Plesial†; Psoradexan; Psoralon MT; Psorispray†; StieLasan†; Warondo Psoriasissalbe†; ***Irl.:*** Psoradrate; ***Ital.:*** Pentagammat†; ***Spain:*** Lapices Epiderm Metadier; Psorantral; ***Switz.:*** Psoradexan; Psoralon MT†; ***UK:*** Dithrolan†; Psoradrate†; Psorin.

Ethyl Lactate (16638-n)

$C_5H_{10}O_3$ = 118.1.
CAS — 97-64-3.

Ethyl lactate has been applied topically in the treatment of acne vulgaris. It is reported to lower the pH within the skin thereby exerting a bactericidal effect.

Ethyl lactate is also used in the flavouring of foods.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***UK:*** Tri-Act†.

Etretinate (1609-s)

Etretinate (*BAN, USAN, rINN*).

Ro-10-9359. Ethyl 3-methoxy-15-apo-ϕ-caroten-15-oate; Ethyl (*all-trans*)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetra-enoate.

$C_{23}H_{30}O_3$ = 354.5.
CAS — 54350-48-0.

Adverse Effects and Precautions

As for Isotretinoin, p.1084.

Donation of blood should be avoided for at least 2 years after cessation of treatment. The period of time during which pregnancy must be avoided following cessation of treatment has not been determined; detectable plasma-etretinate concentrations have been reported nearly 3 years after stopping treatment.

In addition to the references cited below under the various headings, further references to the adverse effects of etretinate can be found in Isotretinoin, p.1084, under Effects on the Blood, Eyes, Liver, Musculoskeletal System, Serum Lipids, and the Skin as well as under Vasculitic Syndromes.

Carcinogenicity. A report of 2 patients developing lymphomas while receiving etretinate[1] prompted a report of 3 other malignancies in patients taking etretinate.[2]

1. Woll PJ, *et al.* Lymphoma in patients taking etretinate. *Lancet* 1987; **ii**: 563–4.
2. Harrison PV. Retinoids and malignancy. *Lancet* 1987; **ii**: 801.

Effects on the cardiovascular system. The Italian Ministry of Health recommended[1] that the electrocardiogram, blood lipids, and clotting factors should be monitored before and throughout treatment with etretinate as there had been rare suspected cases of myocardial ischaemia and infarction reported in treated patients.

1. Anonymous. Reports from regulatory agencies: etretinate. *WHO Drug Inf* 1987; **1**: 29.

Effects on the kidneys. A report of impaired renal function associated with etretinate in one patient.[1] It was noted that in manufacturer-sponsored studies the mean serum-creatinine concentration had been raised in patients receiving etretinate.

1. Horber FF, *et al.* Impaired renal function and hypercalcaemia associated with etretinate. *Lancet* 1984; **ii**: 1093.

Oedema. A report of generalised oedema following treatment with etretinate.[1] Five other cases had been reported in the literature and rechallenge in 4 patients had provoked a recurrence.

1. Allan S, Christmas T. Severe edema associated with etretinate. *J Am Acad Dermatol* 1988; **19**: 140.

Interactions

As for Isotretinoin, p.1085.

Methotrexate. The risk of developing hepatotoxicity may be increased by concomitant administration of etretinate and methotrexate (see Interactions under Methotrexate, p.549).

Warfarin. Etretinate has been reported to reduce the therapeutic efficacy of warfarin (see Interactions under Warfarin, p.968).

Pharmacokinetics

The mean bioavailability of etretinate is about 40% following oral administration but there is a large interindividual variation. Absorption can be increased by administration with milk or fatty food. Etretinate undergoes significant first-pass metabolism and plasma concentrations of the active carboxylic acid metabolite, acitretin (p.1077), may be detected before those of the parent drug; acitretin may itself be metabolised to etretinate (p.1077). Both etretinate and acitretin are extensively bound to plasma protein. Etretinate appears to accumulate in adipose tissue after repeated dosing and has a prolonged elimination half-life of about 120 days; detectable serum concentrations have been observed up to 3 years after the discontinuation of therapy. Up to 75% of a dose is excreted in the faeces mainly as unchanged drug. Etretinate is also excreted in the urine as metabolites. Etretinate crosses the placenta and is distributed into breast milk.

References.

1. Brazzell RK, Colburn WA. Pharmacokinetics of the retinoids isotretinoin and etretinate. *J Am Acad Dermatol* 1982; **6**: 643–51.
2. Rollman O, Vahlquist A. Retinoid concentrations in skin, serum and adipose tissue of patients treated with etretinate. *Br J Dermatol* 1983; **109**: 439–47.
3. Colburn WA, *et al.* Effect of meals on the kinetics of etretinate. *J Clin Pharmacol* 1985; **25**: 583–9.
4. Lucek RW, Colburn WA. Clinical pharmacokinetics of the retinoids. *Clin Pharmacokinet* 1985; **10**: 38–62.
5. DiGiovanna JJ, *et al.* Etretinate: persistent serum levels after long-term therapy. *Arch Dermatol* 1989; **125**: 246–51.

Uses and Administration

Etretinate is a retinoid and is a derivative of tretinoin (p.1093). It has been given by mouth for the treatment of severe, extensive psoriasis that has not responded to other treatment, especially generalised and palmo-plantar pustular psoriasis. It has also been used in severe congenital ichthyosis, and severe Darier's disease (keratosis follicularis) as well as other disorders of keratinisation. Acitretin (p.1077) is now preferred to etretinate.

Therapy has generally been begun at a dosage of 0.75 to 1 mg per kg body-weight daily in divided doses by mouth. A maximum dose of 1.5 mg per kg daily should not be exceeded (some sources have suggested a maximum of 75 mg daily). Erythrodermic psoriasis may respond to lower initial doses of 0.25 mg per kg per day, increased at weekly intervals by 0.25 mg per kg per day until optimal response occurs. Following the initial response, generally after 8 to 16 weeks of therapy, maintenance doses of 0.5 to 0.75 mg per kg daily have been given. Therapy should be discontinued once lesions have sufficiently resolved.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Tigason†; ***Canad.:*** Tegison†; ***Fr.:*** Tigason†; ***Ger.:*** Tigason†; ***Irl.:*** Tigason†; ***Ital.:*** Tigason; ***S.Afr.:*** Tigason†; ***Spain:*** Tigason†; ***Swed.:*** Tigason†; ***Switz.:*** Tigason†; ***UK:*** Tigason†; ***USA:*** Tegison.

Ichthoseptal; Ichthospasmin N†; Pelvichthol N; *Switz.:* Aknichthol N; Ichtho-Cadmin†.

Isotretinoin (1616-p)

Isotretinoin *(BAN, USAN, rINN).*

Isotretinoinum; 13-*cis*-Retinoic Acid; Ro-4-3780. (13*Z*)-15-Apo-β-caroten-15-oic acid; (2*Z*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraenoic acid.

$C_{20}H_{28}O_2$ = 300.4.

CAS — 4759-48-2.

Pharmacopoeias. In *Eur.* (see p.viii) and *US.*

A yellow or light orange, crystalline powder or yellow crystals. Practically **insoluble** in water; sparingly soluble to slightly soluble in alcohol; sparingly soluble in ether, in isopropyl alcohol, and in macrogol 400; soluble in chloroform and in dichloromethane. **Store** in airtight containers at a temperature not exceeding 25°. Protect from light. The Ph. Eur. recommends that the contents of an opened container be used as soon as possible and that any unused part be protected by an atmosphere of an inert gas. The USP specifies that all the contents should be stored under an atmosphere of an inert gas.

Adverse Effects

The adverse effects of isotretinoin and other oral retinoids are similar to those of vitamin A (see p.1358) and are generally reversible and dose-related. The most common are dryness of the mucous membranes and of the skin with scaling, fragility, and erythema, especially of the face, cheilitis, pruritus, epistaxis, conjunctivitis, dry sore mouth, and palmo-plantar exfoliation. Corneal opacities, dry eyes, visual disturbances, skeletal hyperostosis, and musculoskeletal symptoms may also occur. Elevation of serum triglycerides, hepatic enzymes, erythrocyte sedimentation rate, and blood glucose have been reported. Other effects have included hair thinning, photosensitivity, changes in skin pigmentation, paronychia, gastro-intestinal symptoms, headache, drowsiness, sweating, mood changes, psychotic symptoms, depression, suicidal behaviour, benign intracranial hypertension, seizures, vasculitis, and an association with skin infections and an inflammatory bowel syndrome.

Isotretinoin and other retinoids are teratogenic.

When isotretinoin is applied topically the adverse effects are similar to those of tretinoin (see p.1094).

General references.

1. David M, *et al.* Adverse effects of retinoids. *Med Toxicol* 1988; **3:** 273–88.
2. Keefe M. Adverse reactions profile: retinoids. *Prescribers' J* 1995; **35:** 71–6.

Effects on the blood. Thrombocytopenia has been reported in 2 patients receiving etretinate and in one patient treated with isotretinoin.[1] There has also been a report of agranulocytosis associated with isotretinoin therapy in a 16-year-old boy.[2] Leucocytosis[3,4] and multiple thrombosis[5] have been reported in patients who received tretinoin by mouth for treatment of acute promyelocytic leukaemia.

1. Naldi L, *et al.* Etretinate therapy and thrombocytopenia. *Br J Dermatol* 1991; **124:** 395.
2. Waisman M. Agranulocytosis from isotretinoin. *J Am Acad Dermatol* 1988; **18:** 395–6.
3. Toh CH, Winfield DA. All-trans retinoic acid and side-effects. *Lancet* 1992; **339:** 1239–40.
4. Frankel SR, *et al.* The "retinoic acid syndrome" in acute promyelocytic leukemia. *Ann Intern Med* 1992; **117:** 292–6.
5. Forjaz De Lacerda J, *et al.* Multiple thrombosis in acute promyelocytic leukaemia after tretinoin. *Lancet* 1993; **342:** 114–15.

Effects on the eyes. Corneal opacities and papilloedema are among the more serious effects of isotretinoin on the eye but they are usually reversible if therapy is discontinued; papilloedema can result from benign intracranial hypertension[1,2] and patients receiving concomitant treatment with tetracyclines are particularly at risk.[2] Oral retinoids appear to interfere with retinal function[3] and there have been reports of alterations in colour sense,[4] poor night vision, and photophobia.[5] However, a 1-year follow-up failed to find any evidence of ocular toxicity attributable to etretinate in patients who had received long-term treatment and one patient who had toxic optic neuropathy due to methotrexate was able to continue treatment with etretinate.[6]

Ectropion has been associated with etretinate therapy in one patient.[7]

1. Fraunfelder FT, *et al.* Adverse ocular reactions possibly associated with isotretinoin. *Am J Ophthalmol* 1985; **100:** 534–7.
2. Gibberd B. Drug-induced benign intracranial hypertension. *Prescribers' J* 1991; **31:** 118–21.
3. Brown RD, Grattan CEH. Visual toxicity of synthetic retinoids. *Br J Ophthalmol* 1989; **73:** 286–8.
4. Weber U, *et al.* Abnormal retinal function associated with long-term etretinate? *Lancet* 1988; **i:** 235–6.
5. Weleber RG, *et al.* Abnormal retinal function associated with isotretinoin therapy for acne. *Arch Ophthalmol* 1986; **104:** 831–7.
6. Pitts JF, *et al.* Etretinate and visual function: a 1-year follow-up study. *Br J Dermatol* 1991; **125:** 53–5.
7. Brenner S, *et al.* Ectropion: an adverse effect of etretinate therapy for psoriasis. *DICP Ann Pharmacother* 1990; **24:** 1007.

Effects on the liver. Transient slight elevations of serum concentrations of liver enzymes are common with etretinate, but there have been few reports of acute hepatitis[1,2] or cholestatic jaundice.[3] In one patient, acute hepatitis progressed to chronic active hepatitis, despite cessation of etretinate therapy[4] but studies examining serial liver biopsies from patients receiving long-term etretinate have failed to show any significant chronic liver damage.[5-7] The manufacturers have reported instances of hepatic fibrosis, necrosis, and/or cirrhosis.

In a recent overview it was considered that some form of hepatotoxicity may be seen in up to 20% of patients treated with etretinate and significant liver disease is thought to occur in 1%.[8]

Isotretinoin may also cause mild elevations of liver enzymes and the manufacturers state that jaundice and hepatitis have occurred rarely. There is also a report of fatty liver.[9]

1. Foged EK, Jacobsen FK. Side effects due to RO 10-9359 (Tigason). *Dermatologica* 1982; **164:** 395–403.
2. Weiss VC, *et al.* Hepatotoxic reactions in a patient treated with etretinate. *Arch Dermatol* 1984; **120:** 104–6.
3. Gavish D, *et al.* Cholestatic jaundice, an unusual side effect of etretinate. *J Am Acad Dermatol* 1985; **13:** 669–70.
4. Weiss VC, *et al.* Chronic active hepatitis associated with etretinate therapy. *Br J Dermatol* 1985; **112:** 591–7.
5. Glazer SD, *et al.* Ultrastructural survey and tissue analysis of human livers after a 6-month course of etretinate. *J Am Acad Dermatol* 1984; **10:** 632–8.
6. Foged E, *et al.* Histologic changes in the liver during etretinate treatment. *J Am Acad Dermatol* 1984; **11:** 580–3.
7. Roenigk HH, *et al.* Serial liver biopsies in psoriatic patients receiving long-term etretinate. *Br J Dermatol* 1985; **112:** 77–81.
8. Boyd AS. An overview of the retinoids. *Am J Med* 1989; **86:** 568–74.
9. Taylor AEM, Mitchison H. Fatty liver following isotretinoin therapy. *Br J Dermatol* 1991; **124:** 505–6.

Effects on the musculoskeletal system. An ossification disorder resembling diffuse skeletal hyperostosis, with myalgia, arthralgia, and stiffness was first reported by Pittsley in patients who had taken large doses of isotretinoin for prolonged periods.[1] Premature closure of the epiphyses in a child treated with isotretinoin has also been described.[2] DiGiovanna later found radiographic evidence of extraspinal tendon and ligament calcification in patients who had received long-term therapy with etretinate[3] and there were reports of spinal hyperostosis from other workers[4] and one of spinal cord compression.[5] Gilbert *et al.*[6] were unable to find radiographic skeletal changes after 6 to 18 months of treatment with etretinate but Wilson *et al.*[7] found that hyperostosis was fairly common in patients taking moderately prolonged therapy and they recommended that radiological examinations should be carried out every 12 months in patients taking etretinate. However, they were unable to find any clear association between these effects and the total dose or duration of treatment. Others have found evidence of changes after 4 months in patients who had taken isotretinoin 1 mg per kg body-weight daily and recommended that radiological examinations should be made every 6 months in patients receiving isotretinoin for more than a year.[8] However, another study found that although 12% of patients receiving isotretinoin 0.5 mg per kg had evidence of hyperostoses this was not clinically significant in any patient.[9] Tangrea *et al.* suggested that monitoring beyond the treatment period might be unnecessary as calcifications and hyperostosis in patients who had received isotretinoin for 3 years had neither progressed nor improved 10 to 24 months after the end of treatment; additionally no new hyperostoses had developed during that period.[10] Of 25 patients treated with acitretin for a mean of 5 years one had abnormal calcification thought to be caused by the drug;[11] therapy with acitretin was continued with no further side-effects. The authors recommended radiological examinations after twelve months of treatment and then every second year. A study in 135 patients[12] who had received oral retinoids for a mean of 30 months could establish no relationship between spinal abnormalities and prolonged oral retinoid treatment and the authors suggested that spinal abnormalities only occur sporadically in predisposed patients.

There have also been individual reports of hypercalciuria[7] or hypercalcaemia[13-15] associated with oral retinoid therapy. Oral retinoids may also cause muscle damage;[16,17] myositis has been reported with tretinoin[18] and severe myopathy with acitretin.[19]

1. Pittsley RA, Yoder FW. Retinoid hyperostosis: skeletal toxicity associated with long-term administration of 13-cis-retinoic acid for refractory ichthyosis. *N Engl J Med* 1983; **308:** 1012–14.
2. Boone LM, *et al.* Premature epiphyseal closure in a child receiving oral 13-cis-retinoic acid. *J Am Acad Dermatol* 1982; **7:** 663–6.
3. DiGiovanna JJ, *et al.* Extraspinal tendon and ligament calcification associated with long-term therapy with etretinate. *N Engl J Med* 1986; **315:** 1177–82.
4. Archer CB, *et al.* Spinal hyperostosis and etretinate. *Lancet* 1987; **i:** 741.
5. Tfelt-Hansen P, *et al.* Spinal cord compression after long-term etretinate. *Lancet* 1989; **ii:** 325–6.
6. Gilbert M, *et al.* Lack of skeletal radiographic changes during short-term etretinate therapy for psoriasis. *Dermatologica* 1986; **172:** 160–3.
7. Wilson DJ, *et al.* Skeletal hyperostosis and extraosseous calcification in patients receiving long-term etretinate (Tigason). *Br J Dermatol* 1988; **119:** 597–607.
8. Török L, *et al.* Bone-scintigraphic examinations in patients treated with retinoids: a prospective study. *Br J Dermatol* 1989; **120:** 31–6.
9. Carey BM, *et al.* Skeletal toxicity with isotretinoin therapy: a clinico-radiological evaluation. *Br J Dermatol* 1988; **119:** 609–14.
10. Tangrea JA, *et al.* Isotretinoin and the axial skeleton. *Lancet* 1992; **340:** 495–6.
11. Mørk N-J, *et al.* Skeletal side-effects of 5 years' acitretin treatment. *Br J Dermatol* 1996; **134:** 1156–7.
12. Van Dooren-Greebe RJ, *et al.* Prolonged treatment with oral retinoids in adults: no influence on the frequency and severity of spinal abnormalities. *Br J Dermatol* 1996; **134:** 71–6.
13. Valentic JP, *et al.* Hypercalcemia associated with oral isotretinoin in the treatment of severe acne. *JAMA* 1983; **250:** 1899–1900.
14. Horber FF, *et al.* Impaired renal function and hypercalcaemia associated with etretinate. *Lancet* 1984; **ii:** 1093.
15. Akiyama H, *et al.* Hypercalcaemia due to all-trans retinoic acid. *Lancet* 1992; **339:** 308–9.
16. Hodak E, *et al.* Muscle damage induced by isotretinoin. *Br Med J* 1986; **293:** 425–6.
17. David M, *et al.* Electromyographic abnormalities in patients undergoing long-term therapy with etretinate. *J Am Acad Dermatol* 1988; **19:** 273–5.
18. Miranda N, *et al.* Myositis with tretinoin. *Lancet* 1994; **334:** 1096.
19. Lister RK, *et al.* Acitretin-induced myopathy. *Br J Dermatol* 1996; **134:** 989–90.

Effects on the respiratory system. There have been reports of exercise-induced wheezing,[1] eosinophilic pleural effusion,[2] and worsening asthma[3] associated with isotretinoin therapy. The USA manufacturers have records of adverse effects on the lung including worsening asthma, recurrent pneumothorax, interstitial fibrosis, and pulmonary granuloma.[4] A study of healthy subjects confirmed that lung function tests could deteriorate after treatment with isotretinoin.[4]

1. Fisher DA. Exercise-induced bronchoconstriction related to isotretinoin therapy. *J Am Acad Dermatol* 1985; **13:** 524.
2. Bunker CB, *et al.* Isotretinoin and eosinophilic pleural effusion. *Lancet* 1989; **i:** 435–6.
3. Sabroe RA, *et al.* Bronchospasm induced by isotretinoin. *Br Med J* 1996; **312:** 886.
4. Bunker CB, *et al.* Isotretinoin and the lung. *Br J Dermatol* 1991; **125** (suppl 38): 29.

Effects on serum lipids. The oral retinoids induce dose-dependent changes in serum lipids. There can be increases in very-low-density-lipoprotein cholesterol with smaller increases in low-density-lipoprotein cholesterol and reductions in high-density-lipoprotein cholesterol.[1] These effects appear to be unrelated to age or sex. They occur early during treatment and are usually reversible within a few weeks of discontinuation. Overall, the effect of isotretinoin is much greater than that of etretinate. Although the total cholesterol and triglyceride concentrations may remain within normal limits, types IIb and IV hyperlipidaemias are not uncommon among patients receiving oral retinoids. There has been a report of pancreatitis associated with hypertriglyceridaemia in patients treated with isotretinoin.[2]

Retinoids should be used with caution in patients with pre-existing hypertriglyceridaemia or in those at risk of developing hypertriglyceridaemia.[1] Concomitant administration of fish oil containing eicosapentaenoic acid has been reported to attenuate retinoid-induced increases in serum-cholesterol and serum-triglyceride concentrations.[3]

1. Henkin Y, *et al.* Secondary dyslipidemia: inadvertent effects of drugs in clinical practice. *JAMA* 1992; **267:** 961–8.
2. Flynn WJ, *et al.* Pancreatitis associated with isotretinoin-induced hypertriglyceridemia. *Ann Intern Med* 1987; **107:** 63.
3. Marsden JR. Effect of dietary fish oil on hyperlipidaemia due to isotretinoin and etretinate. *Hum Toxicol* 1987; **6:** 219–22.

Effects on sexual function. Ejaculatory failure has been reported in 3 men to be associated with isotretinoin treatment.[1] A possible mechanism could be an effect on the goblet cells of the seminal vesicles, an effect similar to the general reduction in body secretions which leads to dry mucous membranes.

1. Coleman R, MacDonald D. Effects of isotretinoin on male reproductive system. *Lancet* 1994; **344:** 198.

Effects on the skin, hair, and nails. Apart from the more common adverse effects of oral retinoids on the skin and hair (see above), there have been isolated reports of granulomatous lesions,[1,2] precipitation or exacerbation of erythroderma,[3,4] palmo-plantar eruptions,[5] prurigo-like eruptions,[6] scalp folliculitis,[7] pyoderma gangrenosum,[7,8] palmo-plantar stickiness,[9] curling hair,[10] and chloasma (melasma).[11] There has been a report of fatal toxic epidermal necrolysis associated with etretinate.[12] Acne fulminans has been reported as a com-

Pharmacopoeias. Jpn includes berberine chloride and berberine tannate.

A quaternary alkaloid present in hydrastis, in various species of *Berberis*, and in many other plants.

Berberine has been used as a bitter. It possesses antimicrobial activity and has been tried as various salts in a number of infections. Berberine may also be used as a flavouring agent in food and alcoholic drinks.

References.

1. Khin-Maung-U, *et al.* Clinical trial of berberine in acute watery diarrhoea. *Br Med J* 1985; **291**: 1601–5.
2. Rabbani GH, *et al.* Randomized controlled trial of berberine sulfate therapy for diarrhea due to enterotoxigenic Escherichia coli and Vibrio cholerae. *J Infect Dis* 1987; **155**: 979–84.
3. Vennerstrom JL, *et al.* Berberine derivatives as antileishmanial drugs. *Antimicrob Agents Chemother* 1990; **34**: 918–21.
4. Phillipson JD, Wright CW. Medicinal plants in tropical medicine: 1 Medicinal plants against protozoal diseases. *Trans R Soc Trop Med Hyg* 1991; **85**: 18–21.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Murine.

Multi-ingredient: *Fr.:* Pastilles Jessel†; Sedacollyre.

Bergamot Oil (4613-g)

Bergamot Essence; Oleum Bergamottae.

Pharmacopoeias. In *Fr.*

A greenish or brownish-yellow volatile oil with a characteristic fragrant odour and a bitter aromatic taste, obtained by expression from the fresh peel of fruit of *Citrus bergamia* (Rutaceae). Constituents include linalyl acetate and 5-methoxypsoralen.

Bergamot oil is employed in perfumery. It is included in some preparations for upper respiratory-tract disorders. It is also used as a flavouring in Earl Grey tea. It contains 5-methoxypsoralen (p.1088). Photosensitivity reactions have occurred following the topical use of preparations containing bergamot oil.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Belg.:* Ebexol†; *Fr.:* Balsamorhinol; Ephydrol; Humex; *Ger.:* Nephulon E†; *Ital.:* Cura; Sanaderm.

Betahistine Hydrochloride (9213-q)

Betahistine Hydrochloride *(USAN, rINNM).*

Betahistine Dihydrochloride *(BANM)*; PT-9. *N*-Methyl-2-(2-pyridyl)ethylamine dihydrochloride.

$C_8H_{12}N_2,2HCl = 209.1$.

CAS — 5638-76-6 (betahistine); 5579-84-0 (betahistine hydrochloride).

Betahistine Mesylate (10085-v)

Betahistine Mesilate; Betahistini Mesilas. *N*-Methyl-2-(2-pyridyl)ethylamine bismethanesulphonate.

$C_8H_{12}N_2,(CH_4O_3S)_2 = 328.4$.

CAS — 54856-23-4.

Pharmacopoeias. In *Eur.* (see p.viii) and *Jpn.*

A white, crystalline, very hygroscopic powder. Very **soluble** in water; freely soluble in alcohol; very slightly soluble in isopropyl alcohol. A 10% solution in water has a pH of 2 to 3. **Store** in airtight containers.

Adverse Effects

Gastro-intestinal disturbances, headache, and skin rashes have been reported.

Precautions

Betahistine should not be given to patients with phaeochromocytoma. It should be given with care to patients with asthma, peptic ulcer disease or a history of peptic ulcer disease.

Uses and Administration

Betahistine is an analogue of histamine and is claimed to improve the microcirculation of the labyrinth resulting in reduced endolymphatic pressure. It is used to reduce the symptoms of Ménière's disease (p.400).

Betahistine is given by mouth as the hydrochloride or mesylate. The usual initial dose (of the hydrochloride) is 16 mg three times daily taken preferably with meals; maintenance doses are generally in the range of 24 to 48 mg daily. Betahistine mesylate is used in similar doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Aust.: Betaserc; *Austral.:* Serc; *Belg.:* Betaserc; Lobione; *Canad.:* Serc; *Fr.:* Extovyl; Lectil; Serc; *Ger.:* Aequamen; Melopat; Ribrain; Vasomotal; *Irl.:* Serc; *Ital.:* Microser; Vertiserc; *Jpn:* Merislon; *Neth.:* Betaserc; *S.Afr.:* Serc; *Spain:* Fidium; Serc; *Switz.:* Betaserc; *UK:* Serc.

Betaine (16532-j)

Glycine Betaine; Glycocoll Betaine; Lycine; Trimethylglycine. (Carboxymethyl)trimethylammonium hydroxide inner salt.

$C_5H_{11}NO_2 = 117.1$.

CAS — 107-43-7.

Betaine Hydrochloride (1303-j)

Trimethylglycine Hydrochloride. (Carboxymethyl)trimethylammonium hydroxide inner salt hydrochloride.

$C_5H_{11}NO_2,HCl = 153.6$.

CAS — 590-46-5.

Pharmacopoeias. In *Aust., Belg.,* and *US.*

A 25% solution has a pH of 0.8 to 1.2.

Uses and Administration

Betaine is used as a methyl donor to remethylate homocysteine to methionine in the treatment of patients with homocystinuria (p.1330). It is given by mouth in a usual dose of 3 g of anhydrous betaine twice daily. Doses are adjusted according to homocysteine-plasma concentrations; up to 20 g daily has been required in some patients. In children under 3 years old, an initial dose of 100 mg per kg body-weight daily may be used.

Betaine has also been used as a variety of salts in preparations for liver and gastro-intestinal disorders. The hydrochloride has been given as a source of hydrochloric acid in the treatment of hypochlorhydria.

References to betaine use in homocystinuria.

1. Smolin LA, *et al.* The use of betaine for the treatment of homocystinuria. *J Pediatr* 1981; **99**: 467–72.
2. Wilcken DEL, *et al.* Homocystinuria—the effects of betaine in the treatment of patients not responsive to pyridoxine. *N Engl J Med* 1983; **309**: 448–53.
3. Holme E, *et al.* Betaine for treatment of homocystinuria caused by methylenetetrahydrofolate reductase deficiency. *Arch Dis Child* 1989; **64**: 1061–4.
4. Anonymous. Betaine for homocystinuria. *Med Lett Drugs Ther* 1997; **39**: 12.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Cystadane; *Fr.:* Hepagrume; *Ital.:* Ascorbeta†; Somatyl.

Multi-ingredient: *Aust.:* CO_2 Granulat; Oroacid; *Austral.:* Betaine Digestive Aid; Bioglan Digestive Zyme†; Digestaid; Vitaplex Digestive Enzyme Formula†; *Belg.:* Digestomen; Gastrobul†; *Fr.:* Citrarginine; Citro-B_6†; Gastrobul; Liporex†; Nivabetol; Ornitaine; Scorbo-Betaine†; *Ger.:* CO_2 Granulat; Flacar; Unexym MD; Unexym N†; *Ital.:* Beta-Cortex B12†; Betascor B12; Citicortex†; Citroepatina; Epabetina; Equipar†; Fruttidasi†; Glutestere B-Complesso†; Ietepar; *S.Afr.:* Kloref; *Spain:* Digestomen Complex; Espasmo Digestomen; Levaliver; *UK:* Digezyme; Enzyme Digest; Fat-Solv; Kloref; Kloref-S; *USA:* Prevenzyme†.

Bibrocathol (5267-l)

Bibrocathol *(rINN).*

Bibrocathin; Bibrokatol; Bismuth Tetrabrompyrocatechinate; Tetrabromopyrocatechol Bismuth. 4,5,6,7-Tetrabromo-2-hydroxy-1,3,2-benzodioxabismole.

$C_6HBiBr_4O_3 = 649.7$.

CAS — 6915-57-7.

Practically **insoluble** in water.

Bibrocathol is a bismuth-containing compound that has been applied topically in the treatment of eye disorders, wounds, and burns.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Keraform†; *Ger.:* Noviform; Posiformin; *Swed.:* Noviform; *Switz.:* Noviform; Noviforme.

Multi-ingredient: *Ger.:* Lucrusanum†; Noviform-Aethylmorphin†; Novifort.

Bifemelane (1962-m)

Bifemelane *(rINN).*

N-Methyl-4-[(α-phenyl-o-tolyl)oxy]butylamine.

$C_{18}H_{23}NO = 269.4$.

CAS — 90293-01-9.

Bifemelane is a nootropic that has been used in the treatment of senile dementia.

Bile Acids and Salts (998-q)

CAS — 81-25-4 (cholic acid); 11006-55-6 (sodium taurocholate).

Pharmacopoeias. Aust. includes cholic acid. *Jpn* includes bear bile.

The principal primary bile acids, cholic acid and chenodeoxycholic acid (p.1562), are produced in the liver from cholesterol and are conjugated with glycine or taurine to give glycocholic acid, taurocholic acid, glycochenodeoxycholic acid, and taurochenodeoxycholic acid before being secreted into the bile where they are present as the sodium or potassium salts (bile salts). Secondary bile acids are formed in the colon by bacterial deconjugation and 7α-dehydroxylation of cholic acid and chenodeoxycholic acid producing deoxycholic acid and lithocholic acid respectively. Ursodeoxycholic acid (p.1642) is a minor bile acid in man although it is the principal bile acid in *bears*. Dehydrocholic acid (p.1570) is a semisynthetic bile acid.

The total body pool of bile salts is about 3 g, and most of the secreted bile salts are reabsorbed in a process of enterohepatic recycling, so that only a small fraction of this amount must be synthesised *de novo* each day.

Bile salts are strongly amphiphilic; with the aid of phospholipids they form micelles and emulsify cholesterol and other lipids in bile. Oral administration of chenodeoxycholic acid also reduces the synthesis of cholesterol in the liver, while ursodeoxycholic acid reduces biliary cholesterol secretion apparently by increasing conversion of cholesterol to other bile acids. The bile acids (but not the bile salts) also have a choleretic action, increasing the secretion of bile, when given by mouth.

Chenodeoxycholic acid and ursodeoxycholic acid are given by mouth in the management of cholesterol-rich gallstones (p.1642) in patients unsuited to, or unwilling to undergo, surgery. Ursodeoxycholic acid is also under investigation in some liver disorders.

Preparations containing bile salts have been used to assist the emulsification of fats and absorption of fat-soluble vitamins in conditions in which there is a deficiency of bile in the gastro-intestinal tract. Ox bile has also been used in the treatment of chronic constipation.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Proslim-Lipid; *Fr.:* Antimucose; *Ger.:* Cholecysmon; *S.Afr.:* Bilron; *USA:* Bilron†.

Multi-ingredient: *Aust.:* Arca-Enzym; Buccalin; Combizym Compositum; Dragees Neunzehn; Euflat; Festal; Helopanzym; Hylakombun; Nutrizym†; Ozym; Pankreon compositum; Peribilan†; Silberne; Spasmo Gallosanol; *Austral.:* Combizym Co†; Digestaid; Enzyme; Lexat; *Belg.:* Buccaline; Grains de Vals; Pankreon compositum†; Trizymal†; *Canad.:* Aid-Lax; Alsiline; Bicholate; Caroid; Festal†; Herbalax; Herbalax Forte; Laxa; Phytolax; Regubil; Triolax; Vesilax; *Fr.:* Bilifluine; Bilkaby; Festale†; Grains de Vals; Mucinum; Rectopanbiline; *Ger.:* Bilgast†; Bilicombin sp†; Bilipeptal forte†; Cholosom†; Combizym Compositum; Divinal-Bohnen†; Enterotropin†; enzym gallo sanol N†; Enzym-Hepaduran†; Eupond; Gallemolan N†; Gallitophen†; Gallo sanol N†; Gastrocaps†; Glissitol†; Helopanzym†; Hepabionta comp†; Heparaxal†; Hepasteril†; Hepaticum-Divinal†; Hepatofalk Neu; Hylakombun N†; Ludoxin†; Mandrogallan†; Meteophyt-V†; Meteophyt†; Neo-Gallonorm†; Omnadin†; Opobyl†; Pankreatin comp. N†; Pankreon compositum†; Panzynorm forte†; Panzynorm†; Pascopankreat†; Spasmo Gallo Sanol N; Spasmo-Bilicura†; Stomachiagil†; *Ital.:* Bilagar†; Boldosten†; Cheliboldo†; Combizym Compositum†; Enteroton Lassativo†; Enzygaster†; Menabil Complex†; Onoton†; Pancreon Compositum; Reolina†; *Neth.:* Combizym Compositum; Cotazym Forte†; Opobyl†; *S.Afr.:* Nutrizym†; *Spain:* Digestomen Complex; Espasmo Digestomen; Kneipp Pildorast; Laxante Richelet†; Menabil Complex; Pankreon Fuerte†; Secrebil B†; Tornacin†; *Swed.:* Combizym Compositum; Festal†; Pankreon comp. forte†; *Switz.:* Buccaline; Combizym Compositum†; Digestofluid†; Digestozym†; Festal†; Globaset†; Nutrizym†; Opobyl; *UK:* Digezyme; *USA:* Digepepsin; Entozyme†.

Birch Leaf (9616-m)

Betulae Folium; Birkenblätter; Bouleau.

Pharmacopoeias. In *Eur.* (see p.viii) and *Pol.*

The whole or fragmented dried leaves of *Betula pendula (B. verrucosa)* and/or *B. pubescens* as well as hybrids of both species. It contains not less than 1.5% of flavonoids, calculated as hyperoside, with reference to the dried drug. **Protect** from light.

Birch leaf is used in herbal medicine.

Preparations

Proprietary Preparations (details are given in Part 3)
Aust.: Bakanasan Entwasserungs; Galama; Sanhelios-Entwasserungsdragees; *Ger.:* Kneipp Birkenblatter-Pflanzensaft.

Multi-ingredient: *Aust.:* Aktiv Blasen- und Nierentee; Apotheker Bauer's Nieren- und Blasentee; Bio-Garten Entschlackungstee; Bio-Garten Tee fur Niere und Blase; Bio-Garten Tee zur Erhohung der Harnmenge; Bio-Garten Tropfen fur Niere und Blase; Blasen- und Nierentee; Blasentee; Brennesseltonikum; Drogimed; Ehrmann's Entschlackungstee; Entschlackungstee; Fruhjahrs-Elixier ohne Alkohol; Harntreibender Tee; Kneipp Entwasserungstee; Kneipp Nieren- und Blasen-Tee; Krauterdoktor Entwasserungs-Elixier; Krauterhaus Mag Kottas Blasentee; Krauterhaus Mag Kottas Entschlackungstee; Krautertee Nr 19; Krautertee Nr 2; Krautertee Nr 204; Krautertee Nr 25; Krautertee Nr 29; Krautertee Nr 30; Mag Doskar's Nieren- und Blasentonikum; Mag Kottas Entschlackungstee; Rheuma; Sanvita-Entschlackungstonikum; Sidroga Nieren- und Blasentee; Solubitrat; St Radegunder Entwasserungs-Elixier; St Radegunder Entwasserungstee; Synpharma Instant-Blasen-und-Nierentee; Teekanne Blasen- und

Bornyl Acetate (9377-b)

Bornyl Acetate *(USAN)*.

Borneol Acetate. 1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol acetate.

$C_{12}H_{20}O_2$ = 196.3.

CAS — 76-49-3.

Bornyl acetate is a constituent of some essential oils. It has been used in aromatic preparations in the treatment of coughs, other respiratory-tract disorders, and musculoskeletal and joint disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ger.:*** Lindofluid N; ***Ital.:*** Balsamico F. di M.†; ***Spain:*** Vicks Inhalador.

Bromelains (3705-h)

Bromelains *(BAN, USAN, rINN)*.

Bromelins; Plant Protease Concentrate.

CAS — 9001-00-7.

A concentrate of proteolytic enzymes derived from the pineapple plant, *Ananas comosus* (=*A. sativus*) (Bromeliaceae).

Units

One Rorer unit of protease activity has been defined as that amount of enzyme which hydrolyses a standardised casein substrate at pH 7 and 25° so as to cause an increase in absorbance of 0.00001 per minute at 280 nm.

One FIP unit of bromelain activity is reported to be contained in that amount of a standard preparation, which hydrolyses a suitable preparation of casein (FIP controlled) under the standard conditions at an initial rate such that there is liberated per minute an amount of peptides, not precipitated by a specified protein precipitation reagent which gives the same absorbance as 1 μmol of tyrosine at 275 nm.

Activity has also been described in terms of milk-clotting units.

Adverse Effects

Bromelains may cause nausea, vomiting, and diarrhoea. Metrorrhagia and menorrhagia have occasionally occurred. Hypersensitivity reactions have been reported and have included skin reactions and asthma.

Effects on the respiratory system. Bronchial asthma was experienced by 2 patients after exposure to bromelains.[1] Of 6 workers sensitised to papain 5 showed positive skin tests to bromelains and 2 of them also showed immediate asthmatic reactions after bronchial challenge with bromelains.[2]

1. Galleguillos F, Rodriguez JC. Asthma caused by bromelin inhalation. *Clin Allergy* 1978; **8**: 21–4.
2. Baur X, Fruhmann G. Allergic reactions, including asthma, to the pineapple protease bromelain following occupational exposure. *Clin Allergy* 1979; **9**: 443–50.

Precautions

Bromelains should be given with care to patients with coagulation disorders or with severely impaired hepatic or renal function.

Uses and Administration

Bromelains are used as an adjunct in the treatment of soft tissue inflammation and oedema associated with trauma and surgery. Bromelains have also been given as an aid to digestion.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Extranase†; ***Fr.:*** Extranase; ***Ger.:*** Proteozym; Traumanase; ***Irl.:*** Ananase; ***Ital.:*** Ananase; Proteolist†; Rogorint†; ***S.Afr.:*** Ananase; ***Switz.:*** Traumanase; ***USA:*** Dayto-Anase.

Multi-ingredient: ***Aust.:*** Arca-Enzym; Nutrizym†; Wobenzym; ***Austral.:*** Bio-Disc; Bioglan Disconet†; Digestaid; Digestive Aid; Prost-1; Prost-2; Prozyme; Vita Disc†; Vitaplex Digestive Enzyme Formula†; ***Fr.:*** Tetranase; ***Ger.:*** Enzym-Hepaduran†; Enzym-Wied; Esberizym N; Floradix Multipretten; Meteophyt-V†; Mulsal N; Phlogenzym; Traumanase-cyclin†; Wobenzym N; ***Ital.:*** Bres; Convivial†; Debridat Enzimatico†; Derinase Plus; Kilozim†; Plasil Enzimatico†; Prandium†; ***Jpn:*** Kimotab†; ***S.Afr.:*** Haemonase P†; Nutrizym†; ***Spain:*** Bequipecto; Flebo Stop; Tornacin†; Trizima†; ***Switz.:*** Globase†; Nutrizym†; ***UK:*** Cardeymin; Cellbloc†; Digezyme; Enzyme Digest.

Bromine (1022-v)

Bromum.

Br_2 = 159.808.

CAS — 7726-95-6.

A dark reddish-brown, heavy, mobile liquid which gives off intensely irritating brown fumes.

Adverse Effects

Bromine is intensely irritating and corrosive to mucous membranes and, even in dilute solution, may cause fatal gastroenteritis if swallowed. Contact with the skin can produce severe burns and inhalation of the vapour causes violent irritation of the respiratory tract and pulmonary oedema.

Treatment of Adverse Effects

Milk, white of egg, or starch mucilage, taken as soon as possible, have been recommended following ingestion of bromine. If bromine vapour has been inhaled, give assisted respiration, if necessary, and oxygen. Splashes on the skin and eyes should be immediately washed off; washing under running water should continue for at least 15 minutes.

Uses and Administration

Bromine is widely used in industry. It was formerly used, in the form of an adduct with a quaternary ammonium compound in the treatment of plantar warts.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** Callusolve†.

Bryonia (12460-v)

The root of *Bryonia alba* or *B. dioica* (Cucurbitaceae).

Bryonia is an ingredient of preparations used in respiratory-tract infections and inflammatory disorders. It is also used in homoeopathic medicine.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Cough Relief; Harpagophytum Complex; Respatona; Respatona Plus with Echinacea; ***Fr.:*** Quintopan Adult; ***Ger.:*** B 10-Strath†; Bryonia-Strath†; Dolo-Arthrosetten†.

Buchu (12461-g)

Bucco; Buchu Leaves; Diosma; Folia Bucco.

Pharmacopoeias. In *Fr.*

The dried leaves of 'short' or 'round' buchu, *Agathosma betulina* (=*Barosma betulina*) (Rutaceae).

Buchu is a weak diuretic and urinary antiseptic and has been used in multi-ingredient preparations for the treatment of urinary-tract disorders.

Buchu has been used in homoeopathic medicine.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Althaea Complex; De Witt's Pills; Fluid Loss; Herbal Diuretic Complex†; Medinat PMT-Eze; New De Witt's Pills; PMS Support; Serenoa Complex; Urinase; Uva-Ursi Complex; Vitaplex PMT†; ***Belg.:*** Stago†; ***Canad.:*** Herbal Laxative; ***Fr.:*** Saprol†; ***Ger.:*** Buccotean TF†; Buccoteant; Entwasserungs-Tee†; Hevert-Entwasserungs-Tee; Salus Kurbis-Tonikum Compositum†; Urodil N†; Urodil S†; ***S.Afr.:*** Docrub; ***Spain:*** Fagolitos Renal†; ***Switz.:*** Stago†; Urinex (nouvelle formule); ***UK:*** Antitis; Backache Tablets; Buchu Compound; Diuretabs; Herbal Powder No.8†; Kas-Bah; Skin Eruptions Mixture; ***USA:*** Aqua-Rid; Fluidex; Tri-Aqua.

Bucillamine (2897-a)

Bucillamine *(rINN)*.

DE-019; SA-96; Tiobutarit. *N*-(2-Mercapto-2-methylpropionyl)-L-cysteine.

$C_7H_{13}NO_3S_2$ = 223.3.

CAS — 65002-17-7.

Bucillamine is reported to be an immunomodulator used in rheumatoid arthritis.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Rimatil†.

Bucladesine Sodium (18881-v)

Bucladesine Sodium *(rINNM)*.

N-(9-β-D-Ribofuranosyl-9*H*-purin-6-yl)butyramide cyclic 3′,5′-(hydrogen phosphate) 2′-butyrate sodium.

$C_{18}H_{24}N_5O_8PNa$ = 492.4.

CAS — 362-74-3 (bucladesine).

Bucladesine sodium has been reported to have cardiotonic properties. It has been given intravenously. It has also been applied topically for the treatment of bedsores.

Bufotenine (5012-f)

NN-Dimethylserotonin; 5-Hydroxy-*NN*-dimethyltryptamine; Mappine. 3-(2-Dimethylaminoethyl)indol-5-ol.

$C_{12}H_{16}N_2O$ = 204.3.

CAS — 487-93-4.

An indole alkaloid obtained from the seeds and leaves of *Piptadenia peregrina* from which the hallucinogenic snuff, cohoba is prepared, and *P. macrocarpa* (Mimosaceae). It was first isolated from the skin glands of toads (*Bufo* spp.) and has also been isolated from species of *Amanita* (Agaricaceae).

Bufotenine has serotonergic activity and is reported to have hallucinogenic properties. It has no therapeutic use.

Buphenine Hydrochloride (9214-p)

Buphenine Hydrochloride *(BANM)*.

Nylidrin Hydrochloride; Nylidrinium Chloride. 1-(4-Hydroxyphenyl)-2-(1-methyl-3-phenylpropylamino)propan-1-ol hydrochloride.

$C_{19}H_{25}NO_2.HCl$ = 335.9.

CAS — 447-41-6 (buphenine); 849-55-8 (buphenine hydrochloride).

Pharmacopoeias. In *US*.

An odourless, white, crystalline powder. **Soluble** 1 in 65 of water and 1 in 40 of alcohol; slightly soluble in chloroform and ether. A 1% solution in water has a pH of 4.5 to 6.5. **Store** in airtight containers.

Adverse Effects and Precautions

For the adverse effects of sympathomimetics and precautions to be observed, see p.951.

Uses and Administration

Buphenine produces peripheral vasodilatation through beta-adrenoceptor stimulation and a direct action on the arteries and arterioles of the skeletal muscles.

Buphenine has been used in the treatment of disorders of peripheral and cerebral circulatory insufficiency. It has also been used in preparations for rhinitis and nasal congestion. The usual dose of buphenine hydrochloride was 3 to 12 mg by mouth three or four times daily.

An intravenous infusion of buphenine hydrochloride has been used to arrest premature labour. It has also been given orally as a prophylactic tocolytic agent.

Preparations

Proprietary Preparations (details are given in Part 3)
Aust.: Dilatol; Dilydrin; ***Canad.:*** Arlidin; ***Ger.:*** Dilatol†; Penitardon†; ***S.Afr.:*** Dilatol†; ***Spain:*** Diatolil; ***Switz.:*** Dilydrine Retard; Tocodrine; ***USA:*** Arlidin†.

Multi-ingredient: ***Aust.:*** Apoplectal; Arbid; Dilaescol; Dilatol-Chinin; Opino; Tropoderm; ***Belg.:*** Agyrax; ***Fr.:*** Ophtadil; Phlebogel; ***Ger.:*** Apoplectal N; Arbid†; opino heparinoid†; opino N spezial; Rhinoinfant†; ***Ital.:*** Opinot; ***Spain:*** Circovenil; Circovenil Fuerte; Spasmo-Urgenin Rectal†; ***Switz.:*** Arbid; Symfonat; Visaline.

Butinoline Phosphate (11282-a)

Butinoline Phosphate *(rINNM)*.

1,1-Diphenyl-4-pyrrolidino-1′-yl but-2-yn-1-ol phosphate.

$C_{20}H_{21}NO.H_3PO_4$ = 389.4.

CAS — 54118-66-0 (butinoline phosphate); 968-63-8 (butinoline).

Butinoline phosphate is used as an antispasmodic in preparations for gastro-intestinal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Aust.:*** Spasmo-Solugastril; ***Ger.:*** Azulon compositum Homburg†; Jasicholin N; Spasmo-Nervogastrol; Spasmo-Solugastril.

Butyl Nitrite (12483-f)

$C_4H_9NO_2$ = 103.1.

Butyl nitrite is not used medicinally but, as with other volatile nitrites, is abused for its vasodilating and related effects following inhalation (see p.974).

Cadmium (1596-x)

Cd = 112.411.

CAS — 7440-43-9.

Cadmium is employed in a wide range of manufacturing processes and cadmium poisoning presents a recognised industrial hazard. Inhalation of cadmium fume during welding procedures may not produce symptoms until 4 to 10 hours have passed and these symptoms include respiratory distress leading to pulmonary oedema; kidney toxicity is also a feature of cadmium poisoning. Ingestion of cadmium or its salts

treatment of migraine and was an ingredient of a preparation for the premenstrual syndrome.

Fluorescein (2129-n)

Fluorescein (*BAN*).

3',6'-Dihydroxyspiro[isobenzofuran-1(3*H*),9'(9*H*)xanthen]-3-one.

$C_{20}H_{12}O_5$ = 332.3.

CAS — 2321-07-5.

Pharmacopoeias. In *US.*

A colourless yellowish-red to red powder. Practically insoluble in water; soluble in dilute alkali hydroxides. **Store** in light containers.

Fluorescein Dilaurate (1956-v)

Fluorescein Dilaurate (*BANM*).

$C_{44}H_{56}O_7$ = 696.9.

CAS — 7308-90-9.

Fluorescein Sodium (2130-k)

Fluorescein Sodium (*BANM*).

C.I. Acid Yellow 73; Colour Index No. 45350; D & C Yellow No. 8; Fluorescein Natrium; Fluoresceinum Natricum; Obirarin; Resorcinolphthalein Sodium; Sodium Fluorescein; Soluble Fluorescein; Uranin. Disodium fluorescein.

$C_{20}H_{10}Na_2O_5$ = 376.3.

CAS — 518-47-8.

NOTE. FLN is a code approved by the BP for use on single unit doses of eye drops containing fluorescein sodium where the individual container may be too small to bear all the appropriate labelling information. LIDFLN is a similar code approved for eye drops containing lignocaine hydrochloride and fluorescein sodium and PROXFLN a code for eye drops containing proxymetacaine hydrochloride and fluorescein sodium.

Pharmacopoeias. In *Chin., Eur.* (see p.viii), *Int., Jpn,* and *US.*

An orange-red, odourless, fine hygroscopic powder. Freely soluble in water; soluble in alcohol; practically insoluble in hexane and in dichloromethane. A 2% solution in water has a pH of 7.0 to 9.0. **Store** in airtight containers. Protect from light.

Adverse Effects and Precautions

The intravenous injection of fluorescein sodium may produce nausea and vomiting. Extravasation is painful. Hypersensitivity reactions range from urticaria to occasional instances of severe anaphylaxis. Cardiac arrests and fatalities have occurred rarely. Concern that impurities or a defect in manufacturing processes might be responsible for the serious reactions led to a review of the BP specification in the early 1980s and a reduction in the permitted level of impurities.

The skin and urine may be coloured yellow but this is transient. Fluorescein sodium can stain skin, clothing, and soft contact lenses on contact.

Facilities for resuscitation should be available whenever fluorescein sodium is administered intravenously.

Oral fluorescein dilaurate should not be given to patients with acute necrotising pancreatitis. Sulphasalazine may interfere with estimations of fluorescein in the fluorescein dilaurate test.

Two large studies have examined the incidence of adverse reactions following intravenous fluorescein angiography. An international survey[1] collected information concerning 594 687 angiographic procedures; the incidence of serious reactions was 1 in 18 020, and that of fatal reactions, 1 in 49 557. Reactions included anaphylactic shock, cardiac arrest, myocardial infarction, and shock with hypotension or respiratory distress. A USA survey of 221 781 fluorescein angiograms[2] reported frequency rates of 1 in 63 for a moderate reaction (urticaria, syncope, thrombophlebitis, pyrexia, tissue necrosis, or nerve palsy) and 1 in 1900 for severe reactions (respiratory or cardiac events or tonic-clonic seizures); there was one death.

Individual reports of adverse reactions to intravenous fluorescein sodium include pancreatitis,[3] painful crises in patients with sickle-cell disease,[4] and photoallergy[5] and phototoxici-

1. Zografos L. Enquête internationale sur l'incidence des accidents graves ou fatals pouvant survenir lors d'une angiographie fluoresceinique. *J Fr Ophtalmol* 1983; **6**: 495–506.
2. Annunzi LA, *et al.* Fluorescein angiography complication survey. *Ophthalmology* 1986; **93**: 611–17.
3. Regan LH, Martin JM. Acute pancreatitis after fluorescein. *Br Med J* 1983; **287**: 1596.
4. Pearson R, Serjeant G. Painful crises in sickle cell disease after fluorescein angiography. *Lancet* 1985; **1**: 1222.
5. Chasattel R, *et al.* Photoallergic reaction to fluorescein. *Contact Dermatitis* 1990; **22**: 42–4.
6. Thomas GL, *et al.* Fluorescein phototoxicity in a premature infant. *J Pediatr* 1985; **107**: 796–8.

Uses and Administration

Fluorescein sodium stains damaged cornea and ocular fluids and is applied to the eye for the detection of corneal lesions and foreign bodies, as an aid to the fitting of hard contact lenses, and in various other diagnostic ophthalmic procedures. It is applied as a 1 or 2% solution as eye drops or as sterile papers impregnated with fluorescein sodium.

Fluorescein sodium may be given by rapid intravenous injection, usually as a 10 to 25% solution in a dose of 500 mg, for the examination of the ophthalmic vasculature by retinal angiography. A dose of 7.5 mg per kg body-weight has been suggested for children. The oral route has been tried for this purpose. Other uses of intravenous fluorescein sodium have included the differentiation of healthy from diseased or damaged tissue and visualisation of the biliary tract.

Fluorescein dilaurate is given by mouth for the assessment of exocrine pancreatic function (see below). Pancreatic enzymes hydrolyse the ester and the amount of free fluorescein excreted in the urine can therefore be taken as a measure of pancreatic activity. A dose of 348.5 mg of fluorescein dilaurate, equivalent to 0.5 mmol of fluorescein, is given with a standard meal, and urine collected for the following 10 hours. The manufacturers give instructions concerning the type and amount of liquid and food which may be taken during this period. A control dose of 188.14 mg of fluorescein sodium, also equivalent to 0.5 mmol of fluorescein, is given on the following day under the same conditions.

Pancreatic function test. Studies of the fluorescein dilaurate test have considered it to be a useful noninvasive screening test for the exclusion of pancreatic exocrine failure in outpatients, particularly those presenting with steatorrhoea.[1-3] The need for tests such as the pancreozymin-secretin test which requires duodenal intubation may thus be avoided. However, low specificity (a relatively high rate of false-positive responses) has been reported with the fluorescein dilaurate test in some patient populations[2,4] and the need for careful patient instruction in performance of the test has been emphasised.[3]

The test has been used successfully in children,[5] particularly when the doses of fluorescein dilaurate and fluorescein sodium are reduced and fluid intake modified,[6] although the manufacturers recommend that the commercially available test is not used for this age group. In children, a simplified, single day test using dual markers, fluorescein dilaurate and mannitol, has been investigated with encouraging results.[7]

1. Barry RE, *et al.* Fluorescein dilaurate—tubeless test for pancreatic exocrine failure. *Lancet* 1982; **ii**: 742–4.
2. Boyd EJS, *et al.* Prospective comparison of the fluorescein-dilaurate test with the secretin-cholecystokinin test for pancreatic exocrine function. *J Clin Pathol* 1982; **35**: 1240–3.
3. Gould SR, *et al.* Evaluation of a tubeless pancreatic function test in patients with steatorrhoea in a district general hospital. *J R Soc Med* 1988; **81**: 270–3.
4. Braganza JM. Fluorescein dilaurate test. *Lancet* 1982; **ii**: 927–8.
5. Cumming JGR, *et al.* Diagnosis of exocrine pancreatic insufficiency in cystic fibrosis by use of fluorescein dilaurate test. *Arch Dis Child* 1986; **61**: 573–5.
6. Dalzell AM, Heaf DP. Fluorescein dilaurate test of exocrine pancreatic function in cystic fibrosis. *Arch Dis Child* 1990; **65**: 788–9.
7. Green MR, *et al.* Dual marker one day pancreolauryl test. *Arch Dis Child* 1993; **68**: 649–52.

Pediculosis. Infestation of the eye lashes or brows with pubic lice (p.1401) has been successfully treated with a single application of a 20% solution of fluorescein.[1]

1. Mathew M, *et al.* A new treatment of pthiriasis palpebrarum. *Ann Ophthalmol* 1982; **14**: 439–41.

Retinal angiography. Fluorescein is usually given intravenously for retinal angiography but a study in 20 healthy subjects concluded that an oral dose of fluorescein sodium 25 mg per kg body-weight could produce good quality retinal angiograms in the majority of subjects.[1] This study used specially prepared 500-mg capsules of fluorescein sodium; the authors commented that previous oral studies had used the liquid preparation intended for intravenous use. Only mild reactions, possibly due to hypersensitivity, appear to have been reported with oral fluorescein.

1. Watson AP, Rosen ES. Oral fluorescein angiography: reassessment of its relative safety and evaluation of optimum conditions with use of capsules. *Br J Ophthalmol* 1990; **74**: 458–61.

Preparations

BP 1998: Fluorescein Eye Drops; Fluorescein Injection;
USP 23: Fluorescein Injection; Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution; Fluorescein Sodium and Proparacaine Hydrochloride Ophthalmic Solution; Fluorescein Sodium Ophthalmic Strips.

Proprietary Preparations (details are given in Part 3)
Aust.: Fluoftal; ***Austral.:*** Disclo-Plaque; Fluorescite; Fluorets; Ful-Glo; ***Canad.:*** Diofluor; Fluor-I-Strip AT; Fluorescite; Fluorets; Funduscein; ***Irl.:*** Fluorets; ***Ital.:*** Fluoralfa; Pancreolauryl-Test; ***S.Afr.:*** Fluores†; Fluorescite; Fluorets; ***UK:*** Fluorets; ***USA:*** Ak-Fluor; Fluor-I-Strip; Fluorescite; Fluorets; Ful-Glo; Funduscein; Ophthifluor.

Multi-ingredient: ***Aust.:*** Healonid Yellow; Pancreolauryl-Test; ***Austral.:*** Fluress; ***Canad.:*** Dioflur-P†; Fluoracaine; Fluress; Healon Yellow†; ***Ger.:*** Pancreolauryl-Test N; Thilorbin; ***Ital.:*** Healon Yellow; ***Spain:*** Fluotest; Pancreolauryl†; ***Swed.:*** Fluress; Healon Yellow†; ***UK:*** Pancreolauryl-Test; ***USA:*** Flu-Oxinate; Fluoracaine; Flurate; Fluress; Flurox; Healon Yellow.

Formic Acid (1309-x)

Ameisensäure; Aminic Acid; E236; E238 (calcium formate); E237 (sodium formate).

CH_2O_2 = 46.03.

CAS — 64-18-6.

Pharmacopoeias. In *Aust.* and *Pol.*

Formic acid resembles acetic acid in its properties (see p.1541) but is more irritating and pungent. The acid and its sodium and calcium salts are used as preservatives in food. Solutions containing about 60% formic acid have been marketed for the removal of lime scales from kettles. Formic acid has also been used for the removal of tattoos. It is an ingredient of some external preparations promoted for the relief of musculoskeletal and joint disorders, and has been applied in conjunction with benzyl alcohol to aid the removal of nits.

There has been a report of 3 patients who swallowed descaling agents containing 40 or 55% formic acid in which the major complications included local corrosive effects, metabolic acidosis, derangement of blood-clotting mechanisms, and acute onset of respiratory and renal failure.[1] All 3 patients died between 5 to 14 days after admission to hospital. A report of 53 cases of formic acid ingestion included 15 fatalities.[2]

1. Naik RB, *et al.* Ingestion of formic acid-containing agents — report of three fatal cases. *Postgrad Med J* 1980; **56**: 451–6.
2. Rajan N, *et al.* Formic acid poisoning with suicidal intent: a report of 53 cases. *Postgrad Med J* 1985; **61**: 35–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Aust.:*** Aciforin; Berggeist; ***Belg.:*** Euphon; ***Fr.:*** Euphon; ***Ger.:*** Discmigon; Schwefel-Diasporal†; ***Ital.:*** Rubistenol; Rubjovit; ***Switz.:*** Fortalis; ***USA:*** Step 2.

Fosfocreatinine (3794-t)

Fosfocreatinine (*rINN*).

(1-Methyl-4-oxo-2-imidazolidinylidene)phosphoramidic acid.

$C_4H_8N_3O_4P$ = 193.1.

CAS — 5786-71-0 (fosfocreatinine); 19604-05-8 (fosfocreatinine sodium).

Fosfocreatinine or fosfocreatinine sodium has been used in muscle disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Creatergyl†; Sustenium.
Multi-ingredient: ***Fr.:*** Ergadyl†.

Fosforylcholine (12771-x)

Phosphorylcholine. (2-Hydroxyethyl)trimethylammonium chloride dihydrogen phosphate.

$C_5H_{15}ClNO_4P$ = 219.6.

CAS — 107-73-3.

Fosforylcholine is a choleretic that has been used in the treatment of hepatic disorders. The calcium and magnesium salts have also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Heparexine; ***Ital.:*** Epaspest.
Multi-ingredient: ***Ital.:*** Analip†; Fosfolip†.

Fumitory (8880-e)

Erdrauchkraut; Herba Fumariae.

Pharmacopoeias. In *Ger.*

Fumitory comprises the dried or fresh flowering plant *Fumaria officinalis* (Papaveraceae) and is used in herbal medicine. It is an ingredient of preparations used mainly for gastro-intestinal and biliary-tract disorders. Fumitory is also used in homoeopathic medicine.

Preparations

Proprietary Preparations (details are given in Part 3)
Aust.: Bilobene; Oddibil; Oddispasmol; ***Fr.:*** Oddibil; ***Ger.:*** Bilobene; Bomagall mono; Oddibil; ***Spain:*** Colambil.

Multi-ingredient: ***Aust.:*** Hepabene; ***Belg.:*** Tisane Depurative "les 12 Plantes"; ***Fr.:*** Actibil; Actisane Digestion; Bolcitol; Campho-Pneumine Aminophylline†; Depuratif Parnel; Depuratum; Gastralsan; Mediflor Tisane Hypotensive†; Schoum; ***Ger.:*** Choldestal†; Cholongal plus†; Cholongal†; ***Ital.:*** Depurativo; Soluzione Schoum; ***Spain:*** Sol Schoum; ***Switz.:*** Rasayana†; ***UK:*** Skin Cleansing.

† symbol † denotes a preparation no longer actively marketed

In opioid withdrawal lofexidine is given as the hydrochloride in an initial dose of 0.2 mg twice daily by mouth. The dose may be increased gradually by 0.2 to 0.4 mg daily to a maximum of 2.4 mg daily. After 7 to 10 days, or longer in some cases, treatment is withdrawn gradually over at least 2 to 4 days.

Opioid dependence. Washton and colleagues found that 10 of 15 methadone addicts managed with a regimen including lofexidine in doses of 100 μg twice daily to 400 μg four times daily were successfully withdrawn without unacceptable withdrawal symptoms.[1] The findings were similar to those with clonidine but lofexidine appeared to be less sedating and hypotensive. Similar results have been reported by Gold and colleagues,[2] and in a further report by Washton *et al.*[3] A commentary on lofexidine at the time of its launch on the UK market[4] pointed to the lack of clinical data from studies other than from those cited above and hinted at the need for controlled studies on a larger scale.

For a discussion of the treatment of opioid dependence, see p.67.

1. Washton AM, *et al.* Lofexidine, a clonidine analogue effective in opiate withdrawal. *Lancet* 1981; **i:** 991–2.
2. Gold MS, *et al.* Lofexidine, a clonidine analogue effective in opiate withdrawal. *Lancet* 1981; **i:** 992–3.
3. Washton AM, *et al.* Opiate withdrawal using lofexidine, a clonidine analogue with fewer side-effects. *J Clin Psychiatry* 1983; **44:** 335–7.
4. Cox S, Alcorn R. Lofexidine and opioid withdrawal. *Lancet* 1995; **345:** 1385–6.

Preparations

Proprietary Preparations (details are given in Part 3)
UK: Britlofex.

Lorenzo's Oil (14102-f)

Lorenzo's oil is a liquid containing glyceryl trierucate (a source of erucic acid) and glyceryl trioleate (a source of oleic acid), in the ratio one part to four parts respectively. It has been used in conjunction with dietary modification for the treatment of adrenoleucodystrophy, a genetic disorder characterised by demyelination, adrenal cortical insufficiency, and accumulation of saturated 'very-long-chain fatty acids'.

Adrenoleucodystrophy. Adrenoleucodystrophy is a rare X-linked metabolic disorder in which accumulation of saturated very-long-chain fatty acids results in diffuse and multifocal demyelination of the nervous system and adrenocortical insufficiency. The most common form usually affects children and is characterised primarily by cerebral demyelination; it is usually fatal within a few years. In the adult variant, called adrenomyeloneuropathy, demyelination of the spinal cord and peripheral neuropathy progress slowly over many years.

There appears to be no effective treatment for adrenoleucodystrophy or its variants. A high dietary intake of long-chain monounsaturated fatty acids, as provided by the mixture Lorenzo's oil (glyceryl trierucate with glyceryl trioleate), has been tried, the idea being to monopolise the specific enzyme involved in the conversion of long-chain fatty acids to very-long-chain fatty acids. Although dietary therapy with Lorenzo's oil has reduced plasma concentrations of saturated very-long-chain fatty acids there is no evidence that this improves or delays progression of adrenoleucodystrophy or adrenomyeloneuropathy.[1-3] However, it has been suggested that these disorders may not respond to correction of the biochemical abnormality once neurological damage has occurred.[3] The effectiveness of treatment before the appearance of neurological symptoms is currently being studied. There is some evidence to suggest that the childhood form may have an immunological component but results using immunosuppressive agents or immunoglobulins have been reported to be disappointing.[3] Lovastatin can also reduce plasma concentrations of very-long-chain fatty acids.[4]

1. Aubourg P, *et al.* A two-year trial of oleic and erucic acids ("Lorenzo's oil") as treatment for adrenomyeloneuropathy. *N Engl J Med* 1993; **329:** 745–52.
2. Kaplan PW, *et al.* Visual evoked potentials in adrenoleukodystrophy: a trial with glycerol trioleate and Lorenzo oil. *Ann Neurol* 1993; **34:** 169–74.
3. Rizzo WB. Lorenzo's oil—hope and disappointment. *N Engl J Med* 1993; **329:** 801–2.
4. Singh I, *et al.* Lovastatin for X-linked adrenoleukodystrophy. *N Engl J Med* 1998; **339:** 702–3.

Adverse effects. Thrombocytopenia has been reported in patients receiving Lorenzo's oil, although patients are often asymptomatic.[1] It is possible that giant platelets which retain most of their function are produced and that these are not counted by automatic counting procedures giving a false impression of thrombocytopenia.[2]

Lymphocytopenia with an increased incidence of infection has also been reported in few patients.[3]

1. Zinkham WH, *et al.* Lorenzo's oil and thrombocytopenia in patients with adrenoleukodystrophy. *N Engl J Med* 1993; **328:** 1126–7.
2. Stöckler S, *et al.* Giant platelets in erucic acid therapy for adrenoleukodystrophy. *Lancet* 1993; **341:** 1414–15.
3. Unikrig CJ, *et al.* Lorenzo's oil and lymphocytopenia. *N Engl J Med* 1994; **330:** 577.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***UK:*** Lorenzo's Oil.

Lovage Root (11834-e)

Levistici Radix.

Pharmacopoeias. In *Eur.* (see p.viii) and *Pol.*

The whole or cut, dried rhizome and root of *Levisticum officinale*. The whole drug contains not less than 4.0 mL per kg of essential oil and the cut drug not less than 3.0 mL per kg of essential oil, calculated with reference to the anhydrous drug. **Protect** from light.

Lovage root is used in herbal medicine.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Aust.:*** Ehrenhofer-Salbe; Kneipp Stoffwechsel-Unterstutzungs-Tee; Krautertee Nr 19; Krautertee Nr 2; Krautertee Nr 31; ***Ger.:*** Canephron N; Castrophan†; Dr. Kleinschrod's Cor-Insuffin†; Entwasserungs-Tee†; Hevert-Entwasserungs-Tee; Kneipp Schlankheits-Unterstutzungstee†; Nephroselect M; Rheumex†; ***Switz.:*** Tisane antiseptique diuretique†; Tisane diuretique "H"†; ***UK:*** Fragador.

Lupulus (535-f)

Hop Strobile; Hopfenzapfen; Hops; Houblon; Humulus; Lupuli Flos; Lupuli Strobulus; Strobili Lupuli.

Pharmacopoeias. In *Eur.* (see p.viii).

The dried, generally whole, female inflorescences (strobiles) of the hop plant *Humulus lupulus* (Cannabinaceae). **Protect** from light.

Lupulus has been used as a bitter, and supplies the characteristic flavour of beers. It is used in herbal and folk medicine as a sedative. It is also used in homoeopathic medicine.

Preparations

Proprietary Preparations (details are given in Part 3)
Aust.: Zirkulin Beruhigungs-Tee; ***Ger.:*** Bonased-L; Lactidorm.

Multi-ingredient: ***Aust.:*** Aktiv Nerven- und Schlaftee; Bakanasan Einschlaf; Baldracin; Baldrian AMA; Baldrian Dispert Compositum; Baldrian-Elixier; Baldrian-Krautertonikum; Baldriparan Beruhigungs; Beruhigungskapseln; Beruhigungstee; Bio-Garten Tee zur Beruhigung; Bio-Garten Tropfen zur Beruhigung; Biogelat Schlaf; Doppelherz Tonikum; Einschlafkapseln; Hova; Hovaletten†; Krauterdoktor Beruhigungstropfen; Krauterdoktor Entspannungs- und Einschlaftropfen; Krauterdoktor Nerven-Tonikum; Krauterhaus Mag Kottas Nerven- und Schlaftee; Krautertee Nr 1; Krautertee Nr 141; Krautertee Nr 16; Krautertee Nr 201; Luvased; Mag Doskar's Nerventonikum; Mag Kottas Krauterexpress-Nerven-Schlaf-Tee; Mag Kottas Schlaftee; Montana; Nervendragees; Nervenruh; Nerventee; Nervifloran; Phytogran; Sanhelios Einschlaf; Seda-Grandelat; Sidroga Nerven- und Schlaftee; St Radegunder Beruhigungs- und Einschlaftee; St Radegunder Nerven-Tonikum; St Radegunder Nerventee; Vivinox; Wechseltee; ***Austral.:*** Kavosporal†; Migran-ezet†; Pacifenity; Passiflora Complex; Passionflower Plus; Prosed-X; Relaxaplex; Vitaglow Executive Anti Stress†; Vitaglow Herbal Stress†; ***Canad.:*** Herbal Sleep Well†; ***Fr.:*** Santane D_5; Santane N_9; ***Ger.:*** Aranidorm-S; Ardeysedon N; Avedorm; Avedorm N; B 12 Nervinfant†; Baldrian-Dispert Nacht; Baldrianox S; Baldriparan N; Baldriparan stark N; Belladonna-Valobonin†; Beruhigungs-Tee Nervoflux†; Biosedon S; Boxocalm; Bunetten†; Cefasedativ; Cysto Fink; Discmigon; Dormeasan; Dormoverlan; Dr. Klinger's Bergischer Krautertee, Nerven- und Beruhigungstee†; Einschlaf-Kapseln biologisch; Euvegal N†; Gutnacht; Herz-plus Forte N†; Herz-Plus Nerven†; Herz-plus†; Hicoton; Hova†; Hovaletten N; Ivel Schlaf; JuDorm; JuNeuron S; Knufinke Nervenruh Beruhigungs-Tee†; Kytta-Sedativum f; Leukona-Sedativ-Bad; Leukona-Sedativ-Bad sine Chloralhydrat; Luvased; Luvased-Tropfen N; Manns Knoblauch Pillen Plus†; Moradorm S; Nervendragees; Nervenruh†; Nerviguttum†; Nervinetten; Nervinfant N; Nervinfant†; Nervisal†; Nervo.opt†; Nervoregin forte; Neuraston†; Orbis Nerven- und Beruhigungstee†; Pan-Nerventonikum†; Pascosedon S; Phytogran; Presselin K 1 N; Salus Nerven-Schlaf-Tee Nr.22; Salusan; Schupps Baldrian Sedativbad; Seda Kneipp N; Seda-Pasc N†; Seda-Plantina; Sedacur; Sedahopf; Sedaselect N; Sedasyx; Sedatruw S; Sedinfant N; Sediomed S†; Selon; Sensinerv forte; Somnium†; Somnuvis S; Steno-Valocordin†; Stomasal Med; Stomasal†; Valdispert comp; Valeriana comp; Valeriana forte; Valeriana mild; Valeriana-Strath†; Valobonin†; Visinal; Vivinox; Vivinox-Schlafdragees; Worishofener Nervenpflege Dr. Kleinschrod†; ***Switz.:*** Baldriparan; Cysto Fink; Cysto-Caps Chassot; Demonatur Dragees calmantes†; Dicalm†; Dormeasan N; Dormeasan†; Dragees pour le coeur et les nerfs; Dragees pour le sommeil nouvelle formule; Dragees relaxantes et tranquillisantes†; Hyperiforce; Phytoberidin; Phytomed Somni; Soporin; Tisane Natterman instantanee no 6 pour calmer les nerfs et lutter contre l'insomnie†; Tisane pour le coeur et la circulation "H"†; Tisane pour le sommeil et les nerfs; Valobonin†; Valverde Dragees pour le coeur; Valverde Dragees pour le sommeil N; ***UK:*** Ana-Sed; Avena sativa comp.; Becalm; Gerard 99; Kalms; Natrasleep; Newrelax; Night Time; Nytol Herbal; Quiet Days; Quiet Life; Quiet Night; Quiet Nite; Quiet Tyme; Relax B+; Serenity; Somnus; Super Mega B+C; Valerian Compound; Valerina Night-Time.

Lysergide (5011-e)

Lysergide *(BAN, rINN).*

LSD; LSD-25; Lysergic Acid Diethylamide. (+)-*NN*-Diethyl-D-lysergamide; (6a*R*,9*R*)-*NN*-Diethyl-4,6,6a,7,8,9-hexahydro-7-methylindolo[4,3-*fg*]quinoline-9-carboxamide.

$C_{20}H_{25}N_3O$ = 323.4.

CAS — 50-37-3.

Lysergide was formerly used therapeutically but is now encountered as a drug of abuse for its hallucinogenic and psychedelic properties.

There is considerable variation in individual reaction to lysergide. Disorders of visual perception are among the first and most constant reactions to lysergide. Subjects may be hypersensitive to sound. Extreme alterations of mood, depression, distortion of body image, depersonalisation, disorders of thought and time sense, and synaesthesias may be experienced. Anxiety, often amounting to panic, may occur (a 'bad trip'). The effects of lysergide may recur months after ingestion of lysergide; the recurrence or 'flashback' may be spontaneous or induced by alcohol, other drugs, stress, or fatigue.

The subjective effects of lysergide may be preceded or accompanied by somatic effects which are mainly sympathomimetic in nature and include mydriasis, tremor, hyperreflexia, hyperthermia, piloerection, muscle weakness, and ataxia. There may be nausea and vomiting and increased heart rate and blood pressure. Derangement of blood clotting mechanisms has been described. In addition, respiratory arrest, convulsions, and coma may result from overdoses. There is no evidence of fatal reactions to lysergide in man, although accidental deaths, suicides, and homicides have occurred during lysergide intoxication.

Tolerance develops to the behavioural effects of lysergide after several days and may be lost over a similar period. There is cross-tolerance between lysergide, mescaline, and psilocybin and psilocin, but not to amphetamine or to cannabis.

Physical dependence on lysergide does not seem to occur.

Mace Oil (4667-x)

NOTE. Mace has also been used as a name for a tear gas.

A volatile oil obtained by distillation from mace, the arillus of the seed of *Myristica fragrans* (Myristicaceae). **Store** in airtight containers. Protect from light.

Nutmeg (p.1609) is the dried kernel of the seed of *M. fragrans*.

Mace is used as a flavour and carminative similarly to nutmeg (p.1609). It has also been used with herbal substances and other volatile agents in preparations for musculoskeletal and respiratory-tract disorders. As with nutmeg, large doses of mace may cause epileptiform convulsions and hallucinations.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ger.:*** Bormelin†; Reflex-Zonen-Salbe (RZS) (Rowo-333)†; ***Switz.:*** Carmol "blanche"†; Carmol†.

Macrogols (1922-a)

Macrogols *(BAN, rINN).*

PEGs; Polyethylene Glycols; Polyoxyethylene Glycols.

$CH_2(OH)(CH_2OCH_2)_mCH_2OH$. Alternatively some authorities use the general formula $H(OCH_2CH_2)_nOH$ when the number assigned to *n* for a specified macrogol is 1 more than that of *m* in the first formula.

CAS — 25322-68-3 (macrogols); 37361-15-2 (macrogol 300).

Pharmacopoeias. Macrogols of various molecular weights are included in many pharmacopoeias.

Eur. (see p.viii) specifies macrogol 300, 400, 1000, 1500, 3000, 4000, 6000, 20 000, and 35 000. *USNF* has a general monograph describing Polyethylene Glycol which requires that it be labelled with the average nominal molecular weight as part of the official title.

Macrogols are condensation polymers of ethylene oxide and water. Each macrogol name is followed by a number indicating its approximate average molecular weight; thus macrogol 300 has an average molecular weight of about 300 (*m*=5 or 6 giving a molecular weight of 282.3 or 326.4).

Macrogols with an average molecular weight of 200 to 600 are clear to slightly hazy, colourless or almost colourless, viscous liquids with a slight characteristic odour; those with an average molecular weight of more than 1000 are white to off-white solids, also with a slight characteristic odour, which vary in consistency between soft unctuous pastes and hard waxy flakes, beads, or powder. Viscosity increases with increasing molecular weight but hygroscopicity decreases and

Saint-Bernard; Borostyrol; Bronpax; Circulatonic; Eau Precieuse Depensier; Edulcor eucalyptus et mentholt; Ephydrol; Essence Algerienne; Eutalgic; Glyco-Thymoline; Hemagene Tailleur; Inongan; Kamol; Lao-Dal; Lini-Bombe; Lumbalgine; Lysocalm; Myscat; Paps; Pastilles M.B.Ct; Pinorhinol; Pulmoll; Pulmoll au menthol et a l'eucalyptus; Pulveolt; Sacnelt; Sedartryl; Sinex; Sirop Boin; Strepsils Menthol Eucalyptust; Synthol; Tigidol; Valda; Vapo-Myrtol; Vegebom; Vicks Pastilles†; Vicks Soulagilt; Vicks Vaporub; Vicks vitamine C pastilles†; ***Ger.:*** A + B Balsam N; Alferm; Amol Heilkrautergeist N; Anastil†; Anginasin N; Anginetten†; Animbo-N†; Anisan; Asthma-Frenon-S†; Bisolvomed mit Codein†; Bisolvomed†; Bormelin N-Adrenalin†; Bormelint; Bronchicum Tropfen mit Codein†; Bronchodurat; Bronchoforton N†; Broncholind Balsam†; Cobed†; Colomba N†; Cor-Vel; Dalet-Balsam; Denosol; Dolo-Menthoneurin; Dolorsan-Balsam; Dorex†; Efisalin N†; Emser Pastillen echt "Stark"†; Emser Pastillen mit Menthol N; Endrinet; Erkaltungs-Balsam†; Etrat Sportgel; Eufimenth-Balsam N; Fibraflex N†; Fibraflex†; Franzbranntwein; Glutisal-buton-Salbet; Grunlicht Hingfong Essenz; Guakalin†; Hamos N; Heilit Rheuma-Bad N-Kombi†; Heilit Rheuma-Olbad; Hustenstiller N; Influsanbalm†; Inspirol Mundwasser konzentrat; Iosimitant; Keldrin†; Kneipp Brustkaramellen†; Kneipp Fichtennadel Franzbranntwein; Kneipp Herzsalbe Unguentum Cardiacum Kneipp; Koryn†; Leukona-Sauna-Konzentrat†; Lyobalsam N†; Makatussin Balsam mit Menthol; Makinil†; Medichol†; Mentholon Original N; Menthoneurin-Salbe; Mintetten S†; Mucidant; Nasenol-ratiopharm†; Nasivin Intensiv-Balsam†; Neo-Angin N; Nephulon E†; Nervpin N; Night-Care; Optipect mit Kodein†; Optipect N; Optipect Neo; Optipect†; Perflamint†; Pfefferminz-Lysoform; Pin-Alcol; Pinimenthol Bad N; Pinimenthol N; Pinofit†; Pinoidal-Bad†; Praecordin S; Pro-Pecton Balsam†; Probaphen†; Pumilen-Balsam†; Rectosellan N†; Repha-Os; Retterspitz Aerosol; Retterspitz Quick; Rowachol; Rowachol comp.; Rowachol-Digestiv; Rowalind; Salviathymol N; Schupps Fichte-Menthol Olbad; Sedotussin Expectorans; Segmentocut†; Silvapin Aktiv-Tonic MMP†; Sorot-compt; Stas Halstablettent; sulfopecticept†; Tachynerg N; Thymitussin†; Transpulmin E; Trauma-Puren; Trauma-Salbe Rodler 301 N; Tumarol-N; Tussamag Halstabletten; Tussipect; Valomettent; Vipracutan†; Wick Inhalierstift N; Wick Vaporub; Zynedo-K†; ***Irl.:*** Bengue's Balsam; Benylin; Benylin Chesty Cough†; Benylin Childrens Cough; Benylin Decongestant†; Benylin Dry Cough; Benylin Non-Drowsy Chesty Coughs; Benylin with Codeine; Bexalin†; Clonalin; Denorex; Expulin; Karvol; Leotusst; Listerine; Radian-B; Rowachol; Rowalind; Rowatanal; Valda†; Vicks Inhaler; Vicks Vaporub; ***Ital.:*** Abiostil; Antalgola†; Balsamico F. di M.†; Balsamo Italstadium; Balta Intimo Soluzione; Benadryl; Benadryl Complex; Benagol Mentolo-Eucaliptolo; Blefarolin; Bronchenolo Balsamo†; Bronco Valda†; Broncopulmin; Donalg; Efedrocanfine†; Essaproct†; Eucalipto Composto; Fomentil; Golosan†; Herbavit; Lacrime; Lasonil H; Lasoproct; Neo Foille Pomata Disinfettante†; Ondroly-A; Pastiglie Valda; Pinselina Dr. Knapp; Pulmarin; Remy; Respiro; Rinobalsamiche; Rinofil†; Rinogutt Eucalipto-Fher; Rinostil; Rowachol†; Salonpas; Selsun Trattamento†; Sloan; Transpulmina Gel†; Transpulmina Gola; Transpulmina Tosse; Via Mal Trauma Gel; Vicks Cetamium Vit/C†; Vicks Gola†; Vicks Inalante; Vicks Sinex; Vicks Vaporub; ***Mon.:*** Blackoids du Docteur Meur; ***Neth.:*** Agre-Gola; Bronchicum; Bronchofortont; Dampo; Denorex; Menthoneurin; Resdan Rx†; Rhinocaps; Strepsils Menthol en Eucalyptus; Tijgerbalsemt; Tijgeroliet; Vicks Sinex; Vicks Vaporub; ***Norw.:*** Cosylan; ***S.Afr.:*** Allergin; Benylin; Benylin with Codeine; Betalin; Bronchicough; Bronchicum; Bronchicum SB†; Bronchiflu; Bronchilate†; Bronchistop; Cocilix†; Cocillana Co; Coff-Up; Counterpain; Dermoplast†; Diatussin; Difco†; Docrub; Elixirol†; Karvol; Lennaminet; Linctosan; Medituss; Nasomixin; Numzit; Oramond†; Pernicream†; Radian; Respisniffers; Strepsils Eucalyptus Menthol; Strepsils Orange-C; Tussimed; Tussimed Expectorant†; Warm-Up; ***Span:*** Aerospray Analgesico†; Aerospray Antialergico†; Amidoyina†; Analgesico Ut Asens Fn; Angi†; Angiofiline†; Antiseptico Dent Donner†; Amicon; Balsamo Analgesic Karmel; Bartal†; Bellacanfor†; Benadryl Expectorante; Bronquimar; Bronquimar Vit A; Buco Regis; Caltoson Balsamico; Caramelos Agua del Carmen; Caramelos Balsam; Cloroboral; Dentikrisos; Dentol Topico; Dermomycose Talco; Descongestivo Cuve Nasal†; Dol.S Regaliz†; Dolokey; Elixir Dental Formahina†; Eupnol; Gargaril Sulfamida†; Gargaril†; Gartricin; Gingilone Comp†; Hadensa; Ictiomen; Inhalador; Killpan; Kneipp Balsamo; Lapiz Termo Compositum†; Liderflex; Linimento Naion; Magnesia Validada†; Masagil; Mentobox; Mentobox Antitusivo; Mentol Sedans Sulfamidad†; Nani Pre Dental; Orto Nasal; Otogen Calmante; Pastillas Juanola; Pastillas Koki Ment Tivo; Pastillas Vicks Limon†; Pastillas Vicks Mentol†; Pazbronquial; Pinimenthol†; Radio Salil; Reflex; Regal; Respir Balsamico; Rowachol; Ruscus; Sabanotropico; Sartol; Scheriproct; Sinus Inhalaciones; Super Koki†; Synalar Rectal; Synthol†; Talco Antihistam Calber; Termosan; Tyropenicilin R†; Vaselina Mentolada; Vicks Formula 44; Vicks Inhalador; Vicks Spray; Vicks Vaporub; Vitavox Pastillas; Yoguito†; ***Swed.:*** Cosylan; Munvatten†; Otrivin Menthol; Trafuril†; Vicks Vaporub; ***Switz.:*** Alginex†; Alphastria; Angina MCC; Anginol; Artragel; Baume de Chine Temple of Heaven blanc; Baume Esco; Baume Esco Forte; Borostyrol N; Bradoral†; Broncho-Rivo; Bronchocodin; Carmol "blanche"†; Carmol "thermogene"†; Carmol†; Contugel†; Deca; Demo baume; Demo pates pectorales; Demostan; Diabetosan†; Dolo-Menthoneurin†; Eau-de-vie de France avec huile de pin nain du Tirol; Eubucal†; Euproctol; Expectorant Cough Syrup†; Expectoryn Paediatric†; Expectoryn†; Flavangin; Flavovenyl; GEM†; Haemocortin; Haemolan; Histacyl Cutane†; Huile analgesique "Polar-Bar"; Hygiodermil; Makatussin; Makatussin forte; Mirocor†; Nasello; Neo-Angin avec vitamin C exempt de sucre; Neo-Angin exempt de sucre; Noscalin†; Novomint N; Olbas; Pate Iodoforme du Prof Dr Walkhoff; Pectramin; Pharmalyn†; Pinimenthol; Pirom; Pulmex†; Rivolyn†; Roliwol; Saltrates; Sedasept; Sedodermil; Sedotussin; Sloan Baume; Solin S†; Solution ChKM du Prof Dr Walkhoff; Sportusal Spray sine heparino; Stilex; Stix†; Sulgan; Synthol†; Tonex; Tumarol; Tyrothricin; Vicks Formel 44; Vicks Inhaler N; Vicks Sinex; Vicks Vaporub; ***UK:*** Aezodent; Aleevex; Antiseptic Foot Balm; Antiseptic Lozenges; Antiseptic Throat Pastilles; Aspellin; Baby Chest Rub†; Balmosa; Balto Foot Balm; Bengue's Balsam; Benylin Chesty Cough; Benylin Childrens Night Coughs; Benylin Cough & Congestion; Benylin Dry Cough; Benylin Mentholated Linctus; Benylin Non-Drowsy; Benylin Non-Drowsy Chesty Coughs; Benylin with Codeine; Bonjela; Boots Vapour Rub; Buttercup Syrup (Blackcurrant flavour); Buttercup Syrup (Honey and Lemon flavour); Cabdrivers Adult Linctus; Catarrh Pastilles; Chloraseptic†; Colsor; Copholcot; Copholcoids†; Covonia Bronchial Balsam; DDD; Deep Heat Massage; Deep Heat Maximum Strength; Deep Heat Rub; Deep Relief; Denorex; Dermacreme; Dragon Balm; Dubam; Eftab; Expulin; Expulin Paediatric; Expurhint†; Famel Catarrh & Throat Pastilles; Fisherman's Friend Honey Cough Syrup†; Flurex Inhalant†; Frador; Germoloids; Gonne Balm; Guanor; Hill's Balsam Expectorant Pastilles; Hills Balsam Extra Strong; Histalix; Karvol; Lanacane Medicated Powder; Liqufruta Cough Medicine; Listerine Antiseptic Mouthwash; Mac; Melissin; Meltus Expectorant with Decongestant; Mentho-lyptus; Menthol and Wintergreen Heat Product†; Mentholatum Balm†; Mentholatum Nasal Inhaler; Mentholease; Merothol; Nasal Inhaler; Nigroids; Nirolex for Chesty Coughs; Nosor Nose Balm; Olbas; Owbridges for Children†; Penetrol; Phytocil†; Potter's Pastilles; Proctor's Pinelyptus; Radian-B; Ralgex; Rinstead; Rowachol; Salonair; Sanderson's Throat Specific; Snufflebabe; Throaties Catarrh Pastilles; Tiger Balm Liquid; Tiger Balm Red; Tiger Balm White; Tixylix Catarrh; Tixylix Inhalant; Valda; Vapex†; Vapour Rub; Vicks Inhaler; Vicks Sinex; Vicks Vaporub; Vocalzone; Woodwards Baby Chest Rub; ***USA:*** Absorbine Athletes Foot Care; Analgesic Balm; Anbesol; Arthricare Double Ice; Arthricare Odor Free; Arthricare Triple Medicated; Arthritis Hot Creme; Babee; Banadyne-3; Banalg; Ben-Gay; Ben-Gay Ultra; Betuline; BFI; Boil Ease; Calamatum; Campho-Phenique Sting Relief Formula†; Cepacol Maximum Strength; Cepacol Regular Strength; Cepastat; Cepastat Cherry; Chapstick Medicated Lip Balm; Chiggerex; Cool-Mint Listerine; Deep Heating Lotion; Deep Heating Rub; Deep-Down Rub; Denorex; Dermacoat; Dermal-Rub; Dermarest Plus; Dermolin; Eucalyptamint; Flex-all 454; Florida Sunburn Relief; FreshBurst Listerine; Gordobalm; Hall's Sugar Free Mentho-Lyptus; Hawaiian Tropic Cool Aloe with I.C.E.; Icy Hot; Improved Analgesic; infraRUB; Legatrin Rub; Listerine; Massengill; Maximum Strength Flexall 454; Medacote; Medadyne†; Medatussin Plus†; Medicone Derma; Medicone Dressing; Medicone Rectal; Menthacin; Mentholatum Cherry Chest Rub; Mentholatum Natural Ice Lip Protectant; Mentholatum Ointment; MenthoRub; Methalgen; MG Cold Sore Formula; Minit-Rub; MouthKote O/R; Muscle Rub; Musterole; Musterole Extra; N'ice; Nasal Jelly; Orabase Lip; Orasept; Pain Bust-R II; Pain Doctor; Pain X; Panalgesic; Panalgesic Gold; Paralgesic; Pedi-Dri; Pedi-Pro; Pfeiffer's Cold Sore; Phenaseptic†; PrameGel; Rhuli Gel; Rid-a-Pain†; Robitussin Cough Drops; Sarna Anti-Itch; Scalpicin; Schamberg†; Soltice; Sports Spray†; Sting-Kill; Thera-gesic; TiSol; Topic; Tussirex; Vicks Chloraseptic Sore Throat; Vicks Menthol Cough Drops; Vicks Vaporub; Vicks Victors Dual Action Cough Drops; X-Seb T Plus; Ziks; Zonite.

Menyanthes (537-n)

Bitterklee; Bogbean; Buckbean; Folia Trifoli Fibrini; Marsh Trefoil; Trèfle d'Eau.

Pharmacopoeias. In *Aust., Fr.,* and *Pol.*

The dried leaves of the buckbean, *Menyanthes trifoliata* (Menyanthaceae).

Menyanthes has been used as a bitter. It is used in herbal medicine for rheumatic disorders. It is also used in homoeopathic and folk medicine.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Aust.:*** Krauterhaus Mag Kottas Gallen- und Lebertee; Krautertee Nr 9; Mag Kottas Leber-Gallentee; Magentee; Mariazeller; ***Belg.:*** Richelet†; ***Ger.:*** Cefaktivon "novum"; Gallexier; Montana; Nervigutturnt; Ventrodigest†; ***UK:*** Rheumatic Pain; Rheumatic Pain Remedy; Rheumatic Pain Tablets; Vegetex.

Mercuric Chloride (5307-b)

Bicloruro de Mercurio; Cloreto Mercúrico; Corrosive Sublimate; Hydrarg. Perchlor.; Hydrargyri Dichloridum; Hydrargyri Perchloridum; Hydrargyrum Bichloratum; Mercuric Chlor.; Mercurique (Chlorure); Mercury Bichloride; Mercury Perchloride; Quecksilberchlorid.

$HgCl_2 = 271.5$.

CAS — 7487-94-7.

Pharmacopoeias. In *Eur.* (see p.viii).

A heavy, colourless or white, crystalline powder or crystalline masses. **Soluble** 1 in 15 of water, 1 in 3 of alcohol, 1 in 25 of ether, and 1 in 15 of glycerol. A solution in water is acid to litmus. **Protect** from light.

The use of mercuric chloride as an antibacterial substance is limited by its toxicity, its precipitating action on proteins, its irritant action on raw surfaces, its corrosive action on metals, and by the fact that its activity is greatly reduced in the presence of excreta or body fluids.

Details of the adverse effects of mercury compounds are provided under Mercury, below.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Span:*** Lucil†; Oxido Amari; Pantenil; Pomada Pptado Blanc Brum†; Pomada Pptado Blanc Orra†; Resorpil†.

Yellow Mercuric Oxide (5311-d)

Gelbes Quecksilberoxyd; Hydrargyri Oxidum Flavum; Hydrargyri Oxydum Flavum; Mercurique (Oxyde) Jaune; Oxido Amarillo de Mercurio; Yellow Precipitate.

$HgO = 216.6$.

CAS — 21908-53-2.

Pharmacopoeias. In *Belg., Fr.,* and *It.*

An odourless orange-yellow, amorphous powder. Practically **insoluble** in water and in alcohol; soluble in acids.

Yellow mercuric oxide has been used in eye ointments for the local treatment of minor infections including the eradication of pubic lice from the eyelashes. Absorption can occur and produce the adverse effects of inorganic mercury (see below).

Mercuric oxide has been associated with clinical exacerbations of porphyria and is considered unsafe in porphyric patients.[1]

1. Moore MR, McColl KEL. *Porphyria: drug lists.* Glasgow: Porphyria Research Unit, University of Glasgow, 1991.

Pediculosis. Yellow mercuric oxide 1% eye ointment was considered to be a safe and effective treatment in pediculosis (p.1401) of the eyelashes caused by pubic lice (pthiriasis palpebrarum).[1]

1. Ashkenazi I, *et al.* Yellow mercuric oxide: a treatment of choice for phthiriasis palpebrarum. *Br J Ophthalmol* 1991; **75**: 356–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Golden Eye Ointment; ***Fr.:*** Ophtergine†; ***Span:*** Pomada Mercurial†; ***USA:*** Styet.

Multi-ingredient: ***Span:*** Oxido Amari; Pomada Orravan Prec Amart.

Mercurous Chloride (5314-m)

Calomel; Calomelanos; Cloreto Mercuroso; Hydrarg. Subchlor.; Hydrargyri Subchloridum; Hydrargyrosi Chloridum; Hydrargyrum Chloratum (Mite); Mercureux (Chlorure); Mercurius Dulcis; Mercury Monochloride; Mercury Subchloride; Mild Mercurous Chloride; Protocloruro de Mercurio; Quecksilberchlorür.

$HgCl = 236.0$.

CAS — 7546-30-7 (HgCl); 10112-91-1 (Hg_2Cl_2).

Pharmacopoeias. In *Chin.*

Some pharmacopoeias also include Precipitated Mercurous Chloride (Hydrargyri Subchloridum Praecipitatum), a white amorphous powder, to which the synonym 'White Precipitate' (Praecipitatum Album) may be applied. White Precipitate has also been used as a name for Ammoniated Mercury.

Mercurous chloride was formerly given as a laxative and was applied topically as an antibacterial. It was one of the mercury compounds employed in the management of syphilis in the pre-antibiotic era.

The mercurous form of mercury does not possess the corrosive properties of the mercuric form and is not absorbed to any great extent. However, the mercurous form can be converted to the mercuric with consequent toxicity as described under mercury (see below).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***USA:*** Sanitube†.

Mercury (5306-m)

Hydrarg.; Hydrargyrum; Hydrargyrum Depuratum; Mercure; Mercurio; Quecksilber; Quicksilver.

$Hg = 200.59$.

CAS — 7439-97-6.

Pharmacopoeias. In *Aust.* and *Fr.*

A shining, silvery white, very mobile liquid, easily divisible into globules, which readily volatilises on heating.

Adverse Effects

Liquid mercury if ingested is poorly absorbed and, unless there is aspiration or pre-existing gastro-intestinal disorders, is not considered to be a severe toxicological hazard.

The greatest dangers from liquid mercury arise from the inhalation of mercury vapour. On acute exposure, it can cause various gastro-intestinal effects including nausea, vomiting, and diarrhoea; more importantly it is toxic to the respiratory system and this effect can be fatal. Some CNS involvement has also been reported. Liquid mercury is not without its dangers when injected and there have been a number of reports of accidental or intentional parenteral administration. Inorganic

Tics. Tourette's syndrome (p.636) is characterised by motor and vocal tics and behavioural disturbances. Nicotine[1-3] has been reported to be of benefit when used alone or with haloperidol in patients with Tourette's syndrome whose symptoms were not satisfactorily controlled with usual treatment with haloperidol. It is hoped that the use of transdermal nicotine patches will avoid the reported problems of compliance associated with the taste and gastro-intestinal effects of nicotine gum.

1. McConville BJ, *et al.* The effects of nicotine plus haloperidol compared to nicotine only and placebo nicotine only in reducing tic severity and frequency to Tourette's disorder. *Biol Psychiatry* 1992; **31:** 832–40.
2. Silver AA, Sanberg PR. Transdermal nicotine patch and potentiation of haloperidol in Tourette's syndrome. *Lancet* 1993; **342:** 182.
3. Dursun SM, *et al.* Longlasting improvement of Tourette's syndrome with transdermal nicotine. *Lancet* 1994; **344:** 1577.

Ulcerative colitis. The mainstays of treatment for inflammatory bowel disease (p.1171) remain aminosalicylates and corticosteroids. Investigation of the use of nicotine in ulcerative colitis has been prompted by the observation that this condition is rare in smokers. Preliminary results from one study[1] suggested that transdermal nicotine added to conventional maintenance therapy could improve symptoms but a later study[2] found that when used alone nicotine was no more effective than placebo in maintaining remission. Some consider[3] that if further trials do confirm any therapeutic value for nicotine in ulcerative colitis its adverse effects are likely to limit its use in some patients, particularly those who have never smoked. Rectal administration of nicotine is under investigation.[4]

1. Pullan RD, *et al.* Transdermal nicotine for active ulcerative colitis. *N Engl J Med* 1994; **330:** 811–15.
2. Thomas GAO, *et al.* Transdermal nicotine as maintenance therapy for ulcerative colitis. *N Engl J Med* 1995; **332:** 988–92.
3. Rhodes J, Thomas G. Nicotine treatment in ulcerative colitis. *Drugs* 1995; **49:** 157–60.
4. Sandborn WJ, *et al.* Nicotine tartrate liquid enemas for mildly to moderately active left-sided ulcerative colitis unresponsive to first-line therapy: a pilot study. *Aliment Pharmacol Ther* 1997; **11:** 663–71.

Preparations

USP 23: Nicotine Polacrilex Gum; Nicotine Transdermal System.

Proprietary Preparations (details are given in Part 3)
Aust.: Nicolan; Nicorette; Nicotinell; Nicotrol; ***Austral.:*** Nicabate; Nicorette; Nicotinell; Prostep; ***Belg.:*** Nicorette; Nicotinell; ***Canad.:*** Habitrol; Nicoderm; Nicorette; Nicotrol; Prostep; ***Fr.:*** Nicopatch; Nicorette; Nicotinell; Tabazur†; ***Ger.:*** Nicorette; Nicotinell; nikofrenon; ***Irl.:*** Niconil; Nicorette; Nicotinell; ***Ital.:*** Nicorette; Nicotinell TTS; Nicotrans; ***Neth.:*** Nicorette; Nicotinell; ***Norw.:*** Nicorette; Nicotinell; ***S.Afr.:*** Nicorette; Nicotinell TTS; ***Spain:*** Nicodisc; Nicomax; Nicorette; Nicotinell TTS; Nicotrans; Nicotrol; ***Swed.:*** Nicolan; Nicorette; Nicotinell; Nikotugg; Quitt†; ***Switz.:*** Nicorette; Nicostop TTS; Nicotinell; ***UK:*** Nicabate†; Niconil; Nicorette; Nicotinell; NiQuitin CQ; Stubit; ***USA:*** Habitrol; Nicoderm; Nicorette; Nicotrol; Prostep.

Multi-ingredient: ***UK:*** Resolution.

Nitric Acid (1318-r)

Aqua Fortis; Azotic Acid; Nit. Acid; Salpetersäure.
HNO_3 = 63.01.
CAS — 7697-37-2.

Pharmacopoeias. In *Br.* (approximately 70%) and *Pol.* (10%). *Aust.* has Acidum Nitricum Concentratum (64.3 to 66.4%) and Acidum Nitricum (31.1 to 32.2%). Also in *USNF* (69 to 71%).

A clear, colourless or almost colourless, highly corrosive fuming liquid, with a characteristic irritating odour. **Store** in airtight containers.

Adverse Effects and Treatment

As for Hydrochloric Acid, p.1588.

There may be methaemoglobinaemia. Nitric acid stains the skin yellow.

Uses and Administration

Nitric acid has a powerful corrosive action and has been used to remove warts (p.1076), but it should be applied with caution, and less corrosive substances are available. It has also been used for the removal of tattoos.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Ger.:* Solco-Derman; *Switz.:* Solcoderm; Solcogyn.

Nitrobenzene (13025-k)

Nitrobenzol; Oil of Mirbane.
$C_6H_5NO_2$ = 123.1.
CAS — 98-95-3.

A pale yellow liquid with an almond-like odour.

Adverse Effects

Nitrobenzene is highly toxic and the ingestion of 1 g may be fatal. Toxic effects from ingestion are usually delayed for several hours and may include nausea, prostration, burning headache, methaemoglobinaemia with cyanosis, haemolytic anaemia, vomiting (with characteristic odour), convulsions, and coma, ending in death after a few hours. Poisoning may also occur from absorption through the skin, or by inhalation.

Treatment of Adverse Effects

After ingestion of nitrobenzene the stomach should be emptied. Methaemoglobinaemia may be treated with methylene blue. Blood transfusions or haemodialysis may be necessary. Oxygen should be given if cyanosis is severe.

If the skin or eyes are splashed with nitrobenzene, contaminated clothing should be removed immediately and the affected areas washed with running water for at least 15 minutes.

Uses

Nitrobenzene is used in the manufacture of aniline, as a preservative in polishes, and in perfumery and soaps.

Nizofenone (19584-b)

Nizofenone *(rINN).*

Y-9179. 2'-Chloro-2-[2-[(diethylamino)methyl]imidazol-1-yl]-5-nitrobenzophenone.
$C_{21}H_{21}ClN_4O_3$ = 412.9.
CAS — 54533-85-6.

Nizofenone has been used as a nootropic.

Nucleic Acid (15306-t)

Acide Zymonucléique; Acidum Nucleicum; Nucleinic Acid.

A complex mixture of phosphorus-containing organic acids present in living cells.

Nucleic acids are of 2 types, ribonucleic acids (RNA) (see p.1624) and deoxyribonucleic acids (DNA) (see p.1570). They are composed of chains of nucleotides (phosphate esters of purine or pyrimidine bases and pentose sugars).

Since the administration of nucleic acid gives rise to a marked temporary leucocytosis (usually preceded by a short period of leucopenia) it was formerly given in the treatment of a variety of bacterial infections in the hope of enhancing the natural defence mechanisms. Its therapeutic value, however, was never established.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Embrant.

Nutmeg (4679-n)

Muscade; Myristica; Noz Moscada; Nuez Moscada; Nux Moschata.

Pharmacopoeias. In *Chin.*

The dried kernels of the seeds of *Myristica fragrans* (Myristicaceae), containing not less than 5% v/w of volatile oil; the powdered drug contains not less than 4% v/w. Mace (p.1597) is the dried arillus of the seed of *M. fragrans.*

Adverse Effects

Nutmeg, taken in large doses may cause nausea and vomiting, flushing, dry mouth, tachycardia, stimulation of the central nervous system possibly with epileptiform convulsions, miosis, mydriasis, euphoria, and hallucinations. Myristicin and elimicin are thought to be the constituents responsible for the psychotic effects of nutmeg, possibly following metabolism to amphetamine-like compounds.

Some references to the adverse effects of nutmeg.

1. Panayotopoulos DJ, Chisholm DD. Hallucinogenic effect of nutmeg. *Br Med J* 1970; **1:** 754.
2. Faguet RA, Rowland KF. "Spice cabinet" intoxication. *Am J Psychiatry* 1978; **135:** 860–1.
3. Venables GS, *et al.* Nutmeg poisoning. *Br Med J* 1976; **1:** 96.
4. Dietz WH, Stuart MJ. Nutmeg and prostaglandins. *N Engl J Med* 1976; **294:** 503.

Uses and Administration

Nutmeg is the source of nutmeg oil. It is aromatic and carminative and is used as a flavour. Nutmeg has been reported to inhibit prostaglandin synthesis.

It is used in homoeopathic medicine.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Aust.:*** Mariazeller; Schwedenjorg mild; ***Ger.:*** Doppelherz Melissengeist; ***Spain:*** Agua del Carmen; Melisana†; Vicks Vaporub; ***UK:*** Aluminium Free Indigestion; Cough Drops; Melissa comp..

Nutmeg Oil (4678-d)

Ätherisches Muskatöl; Esencia de Nuez Moscada; Essence de Muscade; Essência de Moscada; Myristica Oil; Oleum Myristicae.

Pharmacopoeias. In *Aust., Br., Fr.,* and *Swiss.*

A volatile oil obtained by distillation from nutmeg. It is a clear, colourless, pale yellow or pale green liquid with an odour of nutmeg. It is available as East Indian Nutmeg Oil and West Indian Nutmeg Oil.

East Indian oil is **soluble** 1 in 3 of alcohol (90%), West Indian 1 in 4. **Store** in well-filled containers at a temperature not exceeding 25°. Protect from light.

Nutmeg oil is aromatic and carminative and is used as a flavour. Nutmeg oil and expressed nutmeg oil, a solid fat, are rubefacient.

Preparations

BP 1998: Aromatic Ammonia Spirit *(Sal Volatile Spirit).*

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Aust.:*** Dr Fischers Melissengeist; Emser Nasensalbe; Expectal-Balsam; Pe-Ce; Wick Vaporub; ***Austral.:*** Vicks Vaporub; ***Belg.:*** Melisana†; Vegebom†; Vicks Vaporub; ***Canad.:*** Vaporizing Ointment; ***Fr.:*** Vegebom; Vicks Vaporub; ***Ger.:*** Emser Balsam echt†; Emser Nasensalbe N; Expectal Balsam†; ***S.Afr.:*** Enterodyne; ***Swed.:*** Vicks Vaporub; ***Switz.:*** Carmol "thermogene"†; Carmol†; Roliwol; Vicks Vaporub; ***UK:*** Dragon Balm.

Nux Vomica (538-h)

Brechnuss; Neuz Vómica; Noce Vomica; Noix Vomique; Strychni Semen.
CAS — 357-57-3 (anhydrous brucine).

Pharmacopoeias. In *Aust., Chin., Fr.,* and *Jpn.*
Chin. and *Fr.* also include Powdered Nux Vomica.
Chin. also allows *Strychnos pierriana.*

The dried ripe seeds of *Strychnos nux-vomica* (Loganiaceae).

Nux vomica has the actions of strychnine (see p.1633). Extracts of nux vomica have been used for a wide variety of disorders including those of digestion or debility.

As well as containing strychnine, nux vomica contains brucine which has similar properties.

Nux vomica (Nux vom.) is used in herbal and homoeopathic medicine. Ignatia, the dried seed of *Strychnos ignatii,* is also used in homoeopathic medicine where it is known as Ignatia amara or Iamara.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Belg.:*** Aperop; Digestobiase†; Sanicolax; ***Fr.:*** Creme Rap; Curoveinyl; Digestobiase†; Elixir Grez Chlorhydropepsique†; Quintonine; YSE; YSE Glutamique; ***Ital.:*** Amaro Maffioli†; Enteroton Digestivo†; Lassatina; Pillole Schiast; ***S.Afr.:*** Peter Pote'st; ***Spain:*** Alofedina; ***Switz.:*** Padma-Lax.

Oak Bark (317-l)

Écorce de Chêne; Eichenrinde; Quercus; Quercus Cortex.

Pharmacopoeias. In *Aust., Pol.,* and *Swiss.*

The dried bark from the smaller branches and young stems of the common oak, *Quercus robur* (=*Q. pedunculata*), or the durmast oak, *Q. petraea* (=*Q. sessiliflora*) (Fagaceae).

Oak bark contains quercitannic acid. It has astringent properties and is used in some herbal and homoeopathic preparations. It was formerly used for haemorrhoids and as a gargle.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Silvapin Eichenrinden-Extrakt†; Traxaton.

Multi-ingredient: ***Aust.:*** Menodoron; ***Fr.:*** Tisanes de l'Abbe Hamon no 14; ***Ger.:*** entero sanol†; Pektan N†; Tonsilgon-N; ***Switz.:*** Kernosan Elixir; ***UK:*** Conchae comp.; Menodoron; Peerless Composition Essence.

Octanoic Acid (2597-g)

Octanoic Acid *(USAN, rINN).*
Caprylic Acid.
$CH_3.(CH_2)_6.CO_2H$ = 144.2.
CAS — 124-07-2.

Pharmacopoeias. In *Br.* and *Ger.*

A colourless oily liquid with a characteristic odour. Very slightly **soluble** in water; freely soluble in alcohol; very soluble in acetone and in ether; it dissolves in dilute alcohols.

Sodium Octanoate (3004-t)

Sodium Caprylate.
$C_8H_{15}NaO_2$ = 166.2.
CAS — 1984-06-1.

Pharmacopoeias. In *Ger.*

Pinimenthol; Pommade Kytta†; Thrombocid; ***UK:*** Boots Vapour Rub; Cabdrivers Adult Linctus; Catarrh Pastilles; Karvol; Mentholatum Balm†; Nasal Inhaler; Potter's Pastilles.

Punarnava (13188-y)

Punarnaba.

The fresh or dried plant *Boerhaavia diffusa* (= *B. repens*) (Nyctaginaceae), containing an alkaloid, punarnavine.

Punarnava has been used in India as a diuretic, usually in the form of a liquid extract.

Pyricarbate (13191-p)

Pyricarbate *(rINN).*

Pyridinolcarbamate. 2,6-Pyridinediyldimethylene bis(methylcarbamate).

$C_{11}H_{15}N_3O_4$ = 253.3.

CAS — 1882-26-4.

Pharmacopoeias. In *Fr.* and *Pol.*

Pyricarbate has been given by mouth in the treatment of atherosclerosis and other vascular disorders, hyperlipidaemias, and thrombo-embolic disorders. Adverse effects have included gastro-intestinal disturbances and liver damage.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Angioxil†; Atovert†; Cicloven; Movecil†; Vasagin†; Vasocil†; ***Jpn:*** Anginin; ***Spain:*** Colesterinex; Duvaline†; Esterbiol; Vasmol†.

Multi-ingredient: ***Ital.:*** Clopirt†; Ellemgert†; S.trat.ost†; ***Spain:*** Duvaline Compositum†; Duvaline Flebo†; Esclerobion†.

Pyritinol Hydrochloride (13194-e)

Pyritinol Hydrochloride *(BANM, rINNM).*

Pyrithioxine Hydrochloride. 5,5-Dihydroxy-6,6-dimethyl-3,3-dithiodimethylenebis(4-pyridylmethanol) dihydochloride monohydrate.

$C_{16}H_{20}N_2O_4S_2,2HCl,H_2O$ = 459.4.

CAS — 1098-97-1 (pyritinol); 10049-83-9 (anhydrous pyritinol hydrochloride).

Pharmacopoeias. In *Pol.*

Pyritinol hydrochloride has been described as a nootropic which promotes the uptake of glucose by the brain and has been used in the treatment of various cerebrovascular and mental function disorders. Pyritinol hydrochloride has also been given as an alternative to penicillamine in rheumatoid arthritis. It is given by mouth in a usual dose of 600 mg daily.

References.

1. Martin KJ. On the mechanism of action of Encephabol. *J Int Med Res* 1983; **11**: 55–65.
2. Knezevic S, *et al.* Pyritinol treatment of SDAT patients: evaluation by psychiatric and neurological examination, psychometric testing and rCBF measurements. *Int Clin Psychopharmacol* 1989; **4**: 25–38.

Preparations

Proprietary Preparations (details are given in Part 3)
Aust.: Encephabol; ***Belg.:*** Encephabol†; ***Fr.:*** Encephabol†; ***Ger.:*** Ardeyceryl P; Encephabol; Logomed Neuro-Aktiv-Tabletten; ***Ital.:*** Cerebrotrofina†; Cervitalin†; Encebrovit†; Encefabol; Encerebron†; Maind†; ***S.Afr.:*** Encephabol; ***Spain:*** Bonifen†; ***Switz.:*** Encephabol†.

Multi-ingredient: ***Spain:*** Bonifen B6†; Bonifen Ht; Esclerobion†; Memorino; Plenumil†; Refulgin.

Quassia (539-m)

Bitter Wood; Leño de Cuasia; Quassia Wood; Quassiae Lignum; Quassiaholz.

CAS — 76-78-8 (quassin); 76-77-7 (neoquassin).

Pharmacopoeias. In *Jpn* which allows Jamaican or Surinam quassia.

The dried stem wood of Jamaica quassia, *Picrasma excelsa* (=*Aeschrion excelsa; Picraena excelsa*) (Simaroubaceae) or of Surinam quassia, *Quassia amara* (Simaroubaceae).

Quassia has been used as a bitter. It was formerly given as an enema for the expulsion of threadworms and was applied for pediculosis. It may also be used as a flavour in food, drinks, and confectionery. Extracts of quassia or preparations containing its triterpenoid bitter principle quassin are used to denature alcohol.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Austral.:*** Fisher's Phospherine; ***Belg.:*** Valeria-Fordinet†; ***Fr.:*** Ducase; Quintonine; Spevin; ***Ital.:*** Amaro Maffioli†; Cura; ***Switz.:*** Stomacine; ***UK:*** Sanderson's Throat Specific.

Quinine and Urea Hydrochloride (13201-k)

Carbamidated Quinine Dihydrochloride; Chininum Dihydrochloricum Carbamidatum; Urea-Quinine.

$C_{20}H_{24}N_2O_2,CH_4N_2O,2HCl,5H_2O$ = 547.5.

CAS — 549-52-0 (anhydrous).

Quinine and urea hydrochloride is used for the treatment of haemorrhoidal bleeding and anal fissure. It was formerly used as a local anaesthetic and for the therapeutic actions of quinine.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Kinurea H.

Quinine Ascorbate (13202-a)

Quinine Ascorbate *(USAN).*

Quinine Biascorbate.

$C_{20}H_{24}N_2O_2,2C_6H_8O_6$ = 676.7.

CAS — 146-40-7.

A compound (2 : 1) of ascorbic acid with quinine.

Quinine ascorbate has been used as a smoking deterrent.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Fr.:*** Nicoprive; Paranico; ***Ital.:*** Nicoprive; ***Spain:*** Desinto†.

Rape Oil (7366-p)

Colza Oil; Oleum Rapae; Rapeseed Oil.

Pharmacopoeias. In *Eur.* (see p.viii), *Jpn*, and *Pol.*

The refined fixed oil expressed from the seeds of *Brassica napus* (*Brassica campestris*) var. *oleifera* and certain other species of *Brassica* (Cruciferae). A clear light yellow liquid. Practically **insoluble** in water and in alcohol; miscible with petroleum spirit. It contains not more than 2% of erucic acid. **Store** in well filled airtight containers. Protect from light.

Rape oil has been used in liniments in place of olive oil. It is used in some countries as an edible oil but the erucic acid ($C_{22}H_{42}O_2$=338.6) content of the oil has been implicated in muscle damage. The erucic acid content of oils and fats intended for human consumption and of foodstuffs containing oil or fat is subject to legal control. Contaminated rape oil was the cause of the toxic oil syndrome that affected thousands of Spanish citizens following its distribution in early 1981. There has been some debate as to whether increased frequencies of allergic respiratory symptoms occur in sensitive individuals in areas in which oilseed rape is cultivated.

Raspberry Leaf (13207-d)

Rubi Idaei Folium.

The dried leaflets of *Rubus idaeus* (Rosaceae).

Raspberry leaf contains a principle, readily extracted with hot water, which relaxes the smooth muscle of the uterus and intestine of some *animals.*

Raspberry 'tea' has been a traditional remedy for painful and profuse menstruation and for use before and during confinement. The infusion has also been used as an astringent gargle.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Aust.:*** Bio-Garten Tee gegen Durchfall; Tee gegen Durchfall nach Dr Bohmig†; ***Austral.:*** Rubus Complex; ***Belg.:*** Eugiron; ***Fr.:*** Carbonaphtine Pectineet; ***Ger.:*** Buccoteant; Salus Bronchial-Tee Nr.8; ***UK:*** Helonias Compound.

Red Clover (12167-d)

Cow Clover; Meadow Clover; Purple Clover; Trefoil.

The flowerheads of red clover, *Trifolium pratense* (Leguminosae) have been used in herbal medicine.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Austral.:*** Trifolium Complex.

Relaxin (13208-n)

CAS — 9002-69-1.

A polypeptide hormone extracted from the corpus luteum of the ovaries of pregnant sows. It is reported to be related structurally to insulin and has a molecular weight of about 6000.

Relaxin acts on connective tissue, including collagen, and causes relaxation of the pubic symphysis and softening of the uterine cervix. In many *animal* species it appears to play a major part in cervical ripening before parturition; significant species difference is shown. Relaxin is secreted by the human corpus luteum during pregnancy and is thought to interact with other reproductive hormones. It has been studied for cervical ripening and is under investigation in scleroderma (p.501).

Rhamnose (3921-w)

L-Rhamnose. 6-Deoxy-L-mannose.

$C_6H_{12}O_5$ = 164.2.

CAS — 3615-41-6.

Rhamnose is a monosaccharide used to assess intestinal permeability.

For reference to the use of rhamnose in the differential sugar absorption test, see Lactulose, p.1196.

Rhatany Root (319-j)

Krameria; Krameria Root; Ratanhiae Radix.

Pharmacopoeias. In *Eur.* (see p.viii).

The dried, usually fragmented, underground organs of *Krameria triandra* (Krameriaceae), containing not less than 10% tannins. It is known in commerce as Peruvian rhatany.

The powder is reddish brown. **Protect** from light and humidity.

Rhatany root has astringent properties and is used in herbal and homoeopathic preparations for a variety of disorders, including oropharyngeal inflammation.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Aust.:*** Parodontax; ***Fr.:*** Oxy-thymoline†; ***Ger.:*** Echtrosept-GT†; Repha-Os; ***Ital.:*** Gengivario; ***Spain:*** Encialina; Regal; ***Switz.:*** Eubucal†; ***UK:*** Medicinal Gargle.

Rhus (13210-a)

Sumach Berries.

The dried fruits of the smooth or Pennsylvanian sumach, *Rhus glabra* (Anacardiaceae).

Rhus has astringent and reputed diuretic properties. Poison ivy (*Rhus radicans*) and poison oak (*R. toxicodendron*), species growing in the USA, contain irritant poisons such as urushiol, producing severe contact dermatitis. Extracts of poison ivy and poison oak have been used for the prophylaxis of poison ivy dermatitis but their effectiveness has not been proved.

Poison oak is used in homoeopathic medicine.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ger.:*** C 34-Strath†; Colchicum-Strath†; Hewedolor; Hicoton; Rhus-Rheuma-Gel N.

Ribonuclease (13211-t)

RNase.

CAS — 9001-99-4.

An enzyme present in most mammalian tissue.

Ribonuclease is involved in the catalytic cleavage of ribonucleic acid. It has been applied, alone or in combination with other agents, for its supposed anti-inflammatory properties.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Ribalgilasi†.

Multi-ingredient: ***Fr.:*** Ribatran; ***Ital.:*** Ribociclina.

Ribonucleic Acid (15326-d)

ARN; Plant Nucleic Acid; Ribose Nucleic Acid; RNA; Yeast Nucleic Acid.

Ribonucleic acid is a nucleotide polymer, and 1 of the 2 distinct varieties of nucleic acid (see p.1609). It is found in the cytoplasm and in small amounts in the cell nuclei of living tissues and is directly involved in protein synthesis. It can be extracted from beer or bread yeast. Therapeutically, it has been tried in the treatment of mental retardation and to improve memory in senile dementia and proprietary preparations containing various salts of ribonucleic acid have been advocated for a variety of asthenic and convalescent conditions.

Immune RNA (extracted from the spleens and lymph nodes of immunised animals) has been tried in the immunotherapy of hepatitis and cancer.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Ger.:* durajod†; *Ital.:* Calcio Jodico†; Facovit; Iodo-Calcio-Vitaminico; Polijodurato; Rubidiosin Composto; Rubistenol; Rubjovit.

Rue Oil (4702-q)

Oleum Rutae.

A volatile oil obtained from rue, *Ruta graveolens* (Rutaceae).

Rue oil and infusions of rue were formerly used as antispasmodics and emmenagogues and are reported to have abortifacient properties. Rue is a photosensitiser and the oil is a powerful local irritant.

Rue (Ruta grav.) is used in homoeopathic medicine.

Ruscogenin (3913-w)

(25*R*)-Spirost-5-ene-1β,3β-diol.
$C_{27}H_{42}O_4$ = 430.6.
CAS — 472-11-7.

A sapogenin obtained from butcher's broom, *Ruscus aculeatus* (Liliaceae).

Ruscogenin has been applied in the local treatment of haemorrhoids as rectal ointment or suppositories.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Ruscorectal; *Spain:* Hemodren Simple; Ruscorectal.
Multi-ingredient: *Fr.:* Calmoroide; Proctolog; *Ital.:* Ruscoroid; *Spain:* Abrasone Rectal; Hemodren Compuesto; Neo Analsona; Proctolog; Ruscus; Venacol.

Sabeluzole (2980-y)

Sabeluzole *(BAN, USAN, rINN).*
R-58735. (±)-4-(2-Benzothiazolylmethylamino)-α-[(4-fluorophenoxy)methyl]-1-piperidineethanol.
$C_{23}H_{26}FN_3O_2S$ = 415.5.
CAS — 104153-38-0.

Sabeluzole is a benzothiazole derivative with anticonvulsant and antihypoxic properties. It is under investigation in the treatment of Alzheimer's disease.

Sacrosidase (19809-v)

Sacrosidase is a therapeutic enzyme used for replacement therapy in congenital sucrase-isomaltase deficiency.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Sucraid.

Sage (4704-s)

Feuilles de Sauge; Salbeiblätter; Salvia.

Pharmacopoeias. In *Eur.* (see p.viii) and *Pol.*

Sage is the whole of cut dried leaves of *Salvia officinalis* (Labiatae). The whole drug contains not less than 15 mL per kg and the volatile oil drug not less than 10 mL per kg of an essential oil rich in thujone, both calculated with reference to the anhydrous drug. Protect from light.

Sage has carminative, antispasmodic, antiseptic, and astringent properties and is used as a flavour. It is used in preparations for a wide variety of purposes, including respiratory-tract disorders, gastro-intestinal disorders, and in mouthwashes and gargles for disorders of the mouth and throat. It is also used in homoeopathic medicine.

Preparations

Proprietary Preparations (details are given in Part 3)
Aust.: Salvysat; *Ger.:* Aperisan; Fichtensirup N; Salvysat; Sweatosan N; Viru-Salvysat.
Multi-ingredient: *Aust.:* Apotheker Bauer's Blahungstee; Bronchostop; Cional; Dynexan; Krauterhaus Mag Kottas Wechseltee; Krautertee Nr 10; Krautertee Nr 107; Krautertee Nr 16; Krautertee Nr 311; Krautertee Nr 8; Mentopin; Paradenton; Teekanne Husten- und Brusttee; *Belg.:* Cigarettes Anti-asthmatiques†; Tisane pour Dormir; *Fr.:* Bolcitol; Phytocoltart; Santane V_3; Tisanes de l'Abbe Hamon no 6; *Ger.:* Agamadon; Bronchialtee†; Bronchol-Sud†; Chelidonium-Stratht; Dynexan†; Echtrosept-GT†; entero sanol†; Helago-oel N; Mycatox; Odala wern; Optipect mit Kodein†; Optipect†; Parodontal; Phytpulmon†; Polypharm-Zahnsalbengel N; Presselin 214†; Presselin 52 N; Thymitussin†; Venrovist†; Verus†; Vitosal; Worishofener Leber- und Gallenheilmittel Dr. Kleinschrod†; Worishofener Nieren- und Blasenheilmittel Dr. Kleinschrod†; *Ital.:* Babygellat†; Donalg; Saugella Antisettica†; Saugella Salviettine; *S.Afr.:* Dynexan; *Spain:* Vegetalin; *Switz.:* Anginesin; Cional†; Dynexan; Gynogellat†; Mucosan†; Tisane pectorale et antitussive; Tonex; *UK:* Catarrh; Fragador.

Salverine Hydrochloride (19696-l)

Salverine Hydrochloride *(rINNM).*
M-811 (salverine). 2-[2-(Diethylamino)ethoxy]-benzanilide hydrochloride.
$C_{19}H_{24}N_2O_2$,HCl = 348.9.
CAS — 6376-26-7 (salverine).

Salverine hydrochloride is used as an antispasmodic, usually in combination with other drugs.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Aust.:* Cynarix comp; Montamed; Novipec.

Sambucus (320-q)

Elder Flowers; Fleurs de Sureau; Holunderblüten; Sabugueiro; Sambuc.

Pharmacopoeias. In *Eur.* (see p.viii) and *Pol.*

The dried flowers of *Sambucus nigra* (Caprifoliaceae). **Protect** from light.

Sambucus has astringent, diaphoretic, and anticatarrhal properties and is used in herbal and homoeopathic preparations for a variety of disorders, particularly respiratory-tract disorders. Elder-flower water has been used as a vehicle for eye and skin lotions. Elder-flower ointment has been used as a basis for pomades and cosmetic ointments.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Aust.:* Apotheker Bauer's Grippetee; Bio-Garten Entschlackungstee; Blutreinigungstee†; Bogumil-tassenfertiger milder Abfurtee; Entschlackungstee; Grippetee Dr Zeidler; Grippetee EF-EM-ES; Grippogran; Krauter Hustensaft†; Krauterdoktor Erkaltungstropfen; Krauterhaus Mag Kottas Grippetee; Krautertee Nr 10; Krautertee Nr 2; Krautertee Nr 210; Laxalpin; Mag Kottas Grippe-Tee; Sidroga Erkaltungstee; Sinupret; Sinusol-Schleimlosender Tee; St Radegunder Fiebertee; Teekanne Erkaltungstee; *Austral.:* Sambucus Complex; *Fr.:* Tisane des Familles†; *Ger.:* Abfuhr-Tee Stada†; Grippe-Tee Stada†; Hevert-Erkaltungs-Tee; Hevert-Gicht-Rheuma-Tee comp; Kneipp Rheuma Tee N; Nephrubin; Sinupret; *Ital.:* Sambuco (Specie Composta); *Switz.:* The Brioni; Tisane contre les refroidissements; Tisane laxative H; *UK:* Elder Flowers with Peppermint and Composition Essence; Herb and Honey Cough Elixir; Life Drops; Lifedrops; Sinotar; Tabritis.

Sanguinaria (739-e)

Bloodroot; Red Puccoon; Sanguinaria canadensis; Sanguinarine canadensis; Sanguinaris canadensis.

The dried rhizome of *Sanguinaria canadensis* (Papaveraceae).

Sanguinarine, an alkaloid extracted from *Sanguinaria canadensis*, has been used as an antiplaque agent in toothpaste and mouthwash preparations. Sanguinaria was formerly used as an expectorant but fell into disuse because of its toxicity. Sanguinaria has also been classified by the FDA as a herb that is unsafe for use in foods, beverages, or drugs.

Sanguinaria is used in homoeopathic medicine.

Reviews.

1. Karlowsky JA. Bloodroot: Sanguinaria canadensis L. *Can Pharm J* 1991; **124:** 260, 262–3, 267.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Viadent; *Ital.:* Periogard.
Multi-ingredient: *Austral.:* Lexat; *Canad.:* Mielocol; Viadent; Wampole Bronchial Cough Syrup; *Ital.:* Eudent con Glysan; Periogard.

Sarsaparilla (2408-p)

Salsaparilha; Salsepareille; Sarsa; Sarsaparilla Root; Smilacis Rhizoma.

Pharmacopoeias. In *Chin.* and *Jpn.* which specify *Smilax glabra.*

The dried root of various species of *Smilax* (Liliaceae).

Sarsaparilla, usually in the form of a decoction or extract, has been used as a vehicle and flavour for medicaments. It is also an ingredient of herbal and homoeopathic preparations.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Sarsapsor.
Multi-ingredient: *Austral.:* Esten†; Herbal Cleanse; Proesten; Zestabs†; *Belg.:* Stagot; Tisane Depurative "les 12 Plantes"; *Fr.:* Depuratif Parnel; *Ger.:* Dr. Klinger's Bergischer Krautertee, Abfuhr- und Verdauungstee†; Montana; Pankreaplex N†; Pankreaplex Neu; Pascopankreat†; *Ital.:* Depurativo; Tisana Kelemata; *UK:* Blue Flag Root Compound; Jamaica Sarsaparilla; Ligvites; Skin Eruptions Mixture.

Sassafras Oil (4708-y)

Oleum Sassafras.

A volatile oil distilled from the root or root bark of *Sassafras albidum* (Lauraceae), or from the wood of certain species of *Ocotea* (Lauraceae). It contains safrole.

Sassafras oil has rubefacient properties and was formerly used as a pediculicide. Neither sassafras nor the oil should be taken internally; the use of herb teas of sassafras may lead to a large dose of safrole. The use of safrole in foods has been banned because of carcinogenic and hepatotoxic risks. The use of safrole in toilet preparations is also controlled.

A 47-year-old woman experienced 'shakiness', vomiting, anxiety, tachycardia, and raised blood pressure following ingestion of a potentially fatal dose of sassafras oil (5 mL).[1] Treatment was symptomatic following the use of activated charcoal.

1. Grande GA, Dannewitz SR. Symptomatic sassafras oil ingestion. *Vet Hum Toxicol* 1987; **29:** 447.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Austral.:* Zam-Buk; *Belg.:* Vegebom†; *Fr.:* Vegebom; *S.Afr.:* Zam-Buk; *Spain:* Inhalador; Linimento Klari; Vicks Inhalador.

Saxitoxin (746-w)

Saxitoxin is a neurotoxin associated with paralytic shellfish poisoning. It is an endotoxin produced by species of dinoflagellate plankton present in infected molluscs.

References.

1. Halstead BW, Schantz EJ. *Paralytic shellfish poisoning.* Geneva: WHO, 1984.
2. Aquatic (marine and freshwater) biotoxins. *Environmental Health Criteria 37.* Geneva: WHO, 1984.
3. Hartigan-Go K, Bateman DN. Redtide in the Philippines. *Hum Exp Toxicol* 1994; **13:** 824–30.

Schick Test (8005-j)

Pharmacopoeias. Br. and *US* include standards for Schick test toxin and control.

Schick toxin is prepared from the toxic products of *Corynebacterium diphtheriae.* It should be stored at 2° to 8°. Schick control is Schick toxin that has been inactivated by heat. It should be stored at 2° to 8°.

The Schick test has been used for the diagnosis of susceptibility to diphtheria and, more importantly, to detect patients who might experience an adverse reaction to diphtheria vaccines. Children up to the age of about 8 to 10 years rarely suffer from such reactions following diphtheria vaccination and therefore the Schick test is not usually performed in this age group. In older children and adults a Schick test was formerly used before the use of standard diphtheria vaccines. However, diphtheria vaccines for use in adults and adolescents (p.1507) are now formulated with lesser amounts of toxoid so that the need for prior Schick testing is unnecessary.

A dose of 0.2 mL of the Schick toxin was administered intradermally (intracutaneously) into the flexor surface of the forearm. A similar dose of Schick control was injected into the other forearm. The reaction to the injections was read after 24 to 48 hours, and again after 5 to 7 days to detect late reactors and to confirm a reading taken earlier.

A *negative reaction*, indicating that the patient is immune to diphtheria, occurs when there is no redness at either injection site. A *positive reaction*, indicating susceptibility to diphtheria, occurs as a red flush about 10 mm or more in diameter at the site of injection of the test dose with no reaction to the control injection. A *negative-and-pseudo reaction*, also indicating immunity, is shown by a flush which develops rapidly at each injection site but the reaction fades more rapidly than a positive reaction; the reaction is due to non-specific constituents of the injection. A *combined* or *positive-and-pseudo reaction*, also indicating susceptibility, is shown by a flush which develops rapidly at each injection site, but as it fades a positive reaction develops at the site of the test dose.

Preparations

BP 1998: Schick Control; Schick Test Toxin;
USP 23: Diphtheria Toxin for Schick Test; Schick Test Control.

Strontium Chloride (13270-q)

$SrCl_2.6H_2O = 266.6$.
CAS — 10476-85-4 (anhydrous strontium chloride).

Strontium chloride is used as a 10% toothpaste for the relief of dental hypersensitivity.

Preparations

Proprietary Preparations (details are given in Part 3)
Aust.: Sensodyne med; ***Canad.:*** Sensodyne; ***Switz.:*** Sensodent; ***USA:*** Original Sensodyne; Sensodyne-SC.

Strychnine (542-r)

Estricnina; Strychnina. Strychnidin-10-one.
$C_{21}H_{22}N_2O_2 = 334.4$.
CAS — 57-24-9.

An alkaloid obtained from the seeds of nux vomica (see p.1609) and other species of *Strychnos*.

Strychnine Hydrochloride (543-f)

Strych. Hydrochlor.; Strychninae Hydrochloridum.
$C_{21}H_{22}N_2O_2.HCl.2H_2O = 406.9$.
CAS — 1421-86-9 (anhydrous strychnine hydrochloride); 6101-04-8 (strychnine hydrochloride dihydrate).

Strychnine Nitrate (544-d)

Azotato de Estricnina; Nitrato de Estricnina; Strychninae Nitras; Strychninum Nitricum.
$C_{21}H_{22}N_2O_2.HNO_3 = 397.4$.
CAS — 66-32-0.
Pharmacopoeias. In *Aust.* and *Belg.*

Strychnine Sulphate (546-h)

Strychninae Sulphas; Strychninum Sulfuricum; Sulfato de Estricnina.
$(C_{21}H_{22}N_2O_2)_2.H_2SO_4.5H_2O = 857.0$.
CAS — 60-41-3 (anhydrous strychnine sulphate); 60491-10-3 (strychnine sulphate pentahydrate).
Pharmacopoeias. In *Fr.*

Adverse Effects

The symptoms of strychnine poisoning are mainly those arising from stimulation of the CNS. Early signs occurring within 15 to 30 minutes of ingestion include tremors, slight twitching, and stiffness of the face and legs. Painful convulsions develop and may be triggered by minor sensory stimuli; since consciousness is not impaired patients may be extremely distressed. All forms of sensation are heightened. The body becomes arched backwards in hyperextension with the head retracted, arms and legs extended, fists clenched, and the feet turned inward. The jaw is rigidly clamped and contraction of the facial muscles produces a characteristic grinning expression known as 'risus sardonicus'. The convulsions may recur repeatedly and are interspersed with periods of relaxation. If not treated adequately, few patients survive more than 5 episodes of convulsions, death usually occurring due to respiratory arrest. Fatalities have occurred with doses as little as 16 mg.

Secondary effects arising from the severe spasms include lactic acidosis, rhabdomyolysis, renal failure, hyperthermia, hyperkalaemia, and dehydration.

Some references to strychnine poisoning.

1. O'Callaghan WG, *et al.* Unusual strychnine poisoning and its treatment: report of eight cases. *Br Med J* 1982; **285:** 478.
2. Blain PG, *et al.* Strychnine poisoning: abnormal eye movements. *J Toxicol Clin Toxicol* 1982; **19:** 215–17.
3. Boyd RE, *et al.* Strychnine poisoning: recovery from profound lactic acidosis, hyperthermia, and rhabdomyolysis. *Am J Med* 1983; **74:** 507–12.
4. Burn DJ, *et al.* Strychnine poisoning as an unusual cause of convulsions. *Postgrad Med J* 1989; **65:** 563–4.

Treatment of Adverse Effects

The main object of therapy in strychnine poisoning is the prompt prevention or control of convulsions and asphyxia. Patients should be given activated charcoal. Convulsions should be controlled or prevented by diazepam. Should diazepam fail then muscle relaxants should be tried together with intubation and assisted respiration. Gastric lavage should only be carried out when the patient is no longer at risk from convulsions. All unnecessary external stimuli should be avoided and if possible the patient should be kept in a quiet darkened room. Patients should be monitored for any secondary effects from the convulsions so that appropriate symptomatic treatment can be given.

Uses and Administration

Strychnine competes with glycine which is an inhibitory neurotransmitter; it thus exerts a central stimulant effect through blocking an inhibitory activity.

Strychnine was formerly used as a bitter and analeptic but is now mainly used under strict control as a rodenticide, or as a mole poison. It has been used in multi-ingredient preparations for the treatment of ophthalmic and urinary-tract disorders. It has also been tried in the treatment of nonketotic hyperglycinaemia.

Nonketotic hyperglycinaemia. Nonketotic hyperglycinaemia is an inborn defect in the enzyme system responsible for the metabolism of glycine. It is characterised by raised concentrations of glycine in plasma, CSF, and urine. Symptoms of glycine accumulation include respiratory distress, muscular hypotonia, seizures, vomiting, and extreme lethargy. Mental retardation and early infant death are common.

Sodium benzoate has been reported to be effective in reducing plasma-glycine concentrations to near normal but is relatively ineffective in reducing CSF levels or in preventing mental retardation.[1] Strychnine, a glycine antagonist, has been of some benefit in counteracting the effects of high concentrations of glycine in the CNS.[2-4] However, some reports suggest that even concomitant treatment with sodium benzoate and strychnine may be ineffective in severe forms[5] and may ultimately have little effect on the course of the disease.[6] The combination of strychnine and ketamine (a N-methyl-D-aspartate receptor antagonist) was of some benefit in a newborn infant with severe nonketotic hyperglycinaemia.[7] Addition of low-dose dextromethorphan to treatment with sodium benzoate, arginine, carnitine, diazepam, and phenobarbitone in an infant with nonketotic hyperglycinaemia[8] was associated with resolution of nystagmus and improvement in eye contact and interactive behaviour, without altering serum- or CSF-glycine concentrations. Dextromethorphan with sodium benzoate alone may also be helpful, although the combination is not uniformly effective.[9]

1. Krieger I, *et al.* Cerebrospinal fluid glycine in nonketotic hyperglycinemia: effect of treatment with sodium benzoate and a ventricular shunt. *Metabolism* 1977; **26:** 517–24.
2. Ch'ien LT, *et al.* Glycine encephalopathy. *N Engl J Med* 1978; **298:** 687.
3. Gitzelmann R, *et al.* Strychnine for the treatment of nonketotic hyperglycinaemia. *N Engl J Med* 1978; **298:** 1424.
4. Arneson D, *et al.* Strychnine therapy in nonketotic hyperglycinemia. *Pediatrics* 1979; **63:** 369–73.
5. Sankaran K, *et al.* Glycine encephalopathy in a neonate. *Clin Pediatr (Phila)* 1982; **21:** 636–7.
6. MacDermot KD, *et al.* Attempts at use of strychnine sulfate in the treatment of nonketotic hyperglycinemia. *Pediatrics* 1980; **65:** 61–4.
7. Tegtmeyer-Metzdorf H, *et al.* Ketamine and strychnine treatment of an infant with nonketotic hyperglycinaemia. *Eur J Pediatr* 1995; **154:** 649–53.
8. Alemzadeh R, *et al.* Efficacy of low-dose dextromethorphan in the treatment of nonketotic hyperglycinemia. *Pediatrics* 1996; **97:** 924–6.
9. Hamosh A, *et al.* Long-term use of high-dose benzoate and dextromethorphan for the treatment of nonketotic hyperglycinemia. *J Pediatr* 1998; **132:** 709–13.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Aust.:*** Dysurgal; ***Fr.:*** Pastilles Jesselt†; ***Ital.:*** Neuroftal; Retinovix†.

Suanzaorentang (985-h)

Ziziphus Soup.

Suanzaorentang is an ancient Chinese remedy for anxiety and insomnia. It contains five herbs: suanzaoren (*Zizyphus spinosus* of the Rhamnaceae), fuling (*Poria cocos* of the Polyporaceae), gancao (*Glycyrrhiza uralensis* of the Leguminosae), zhimu (*Anemarrhena asphodeloides* of the Liliaceae), and chuanxiong (*Ligusticum chuanxiong* of the Umbelliferae).

Succinimide (13271-p)

Butanimide. Pyrrolidine-2,5-dione.
$C_4H_5NO_2 = 99.09$.
CAS — 123-56-8.

Succinimide has been claimed to inhibit the formation of oxalic acid calculi in the kidney and to reduce hyperoxaluria.

It has been given by mouth in doses of 3 g two or three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Orotric.

Sucrose Octa-acetate (13273-w)

Sucrose Octaacetate.
$C_{28}H_{38}O_{19} = 678.6$.
CAS — 126-14-7.
Pharmacopoeias. In *USNF.*

A white, practically odourless, hygroscopic powder with an intensely bitter taste. **Soluble** 1 in 1100 of water, 1 in 11 of alcohol, 1 in 0.3 of acetone, and 1 in 0.5 of toluene; soluble in ether; very soluble in chloroform and in methyl alcohol. **Store** in airtight containers.

Sucrose octa-acetate has been used as an alcohol denaturant. It is also incorporated into preparations intended to deter nail biting.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Austral.:*** Bansuk†; ***Spain:*** Morde X; ***USA:*** Don't.

Sulphan Blue (2150-r)

Sulphan Blue *(BAN).*
Acid Blue 1; Alphazurine 2G; Blue VRS; Colour Index No. 42045; Isosulfan Blue *(USAN)*; P-1888; P-4125; Patent Blue V; Sulphanum Caeruleum. Sodium α-(4-diethylaminophenyl)-α-(4-diethyliminiocyclo-hexa-2,5-dienylidene)toluene-2,5-disulphonate.
$C_{27}H_{31}N_2NaO_6S_2 = 566.7$.
CAS — 68238-36-8; 129-17-9 (2,4-disulphonate isomer).

NOTE. The name Patent Blue V is mainly used for CI No. 42051 (p.1616). Sulphan blue was formerly described as the 2,4-disulphonate isomer.

Sulphan blue is reported to be **incompatible** with lignocaine.

Adverse Effects and Precautions

Sulphan blue occasionally causes nausea. Hypersensitivity reactions and attacks of asthma have been reported.

Sulphan blue should not be used during surgical shock. Sulphan blue has been reported to interfere with blood tests for protein and iron.

Hypersensitivity. References.

1. Hepps S, Dollinger M. Anaphylactic death after administration of a triphenylmethane dye to determine burn depth. *N Engl J Med* 1965; **272:** 1281.
2. Longnecker SM, *et al.* Life-threatening anaphylaxis following subcutaneous administration of isosulfan blue 1%. *Clin Pharm* 1985; **4:** 219–21.

Uses and Administration

Changes in skin colour occur 60 to 90 seconds after an intravenous injection of sulphan blue and complete body staining is established in 3 to 5 minutes. This effect has been used as a direct visual test of the state of the circulation in healthy and damaged tissues, particularly in assessing tissue viability in burns and soft-tissue trauma.

Sulphan blue given subcutaneously has been used in lymphangiography to outline the lymph vessels.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Lymphazurin.

Sulphobromophthalein Sodium (2151-f)

Sulphobromophthalein Sodium *(BANM).*
Bromsulfophthalein Sodium; Bromsulphthalein Sodium; BSP; SBP; Sodium Sulfobromophthalein; Sulfobromophthalein Sodium. Disodium 4,5,6,7-tetrabromophenolphthalein-3',3''-disulphonate; Disodium 5,5'-(4,5,6,7-tetrabromophthalidylidene)bis(2-hydroxybenzenesulphonate).
$C_{20}H_8Br_4Na_2O_{10}S_2 = 838.0$.
CAS — 297-83-6 (sulphobromophthalein); 71-67-0 (sulphobromophthalein sodium).
Pharmacopoeias. In *It.* and *Jpn.*

In patients with normal hepatic function sulphobromophthalein sodium is rapidly extracted, conjugated, and excreted in bile. It was formerly used intravenously as a diagnostic agent for testing the functional capacity of the liver but may cause severe hypersensitivity reactions.

Sulphuric Acid (1325-x)

513; Acid. Sulph. Conc.; Oil of Vitriol; Schwefelsäure; Sulfuric Acid.
$H_2SO_4 = 98.08$.
CAS — 7664-93-9.
Pharmacopoeias. In *Aust., Br.,* and *Fr.* Also in *USNF.*

A clear colourless corrosive liquid of oily consistence. **Miscible** with water and with alcohol. Much heat is evolved when sulphuric acid is added to other liquids. Concentrated oil of vitriol of commerce, 'COV', contains about 95 to 98% w/w, and brown oil of vitriol, 'BOV', contains 75 to 85% w/w of H_2SO_4. Nordhausen or fuming sulphuric acid, 'Oleum', is sulphuric acid containing SO_3; battery or accumulator acid is sulphuric acid diluted with distilled water to a specific gravity of 1.2 to 1.26.

Store in airtight containers.

CAUTION. *When sulphuric acid is mixed with other liquids, it should always be added slowly, with constant stirring, to the diluent.*

References.
1. Nicholls A, *et al.* Effect of BW12C on lactate levels during exercise in healthy volunteers. *Br J Clin Pharmacol* 1989; **28:** 747P.
2. Philip PA, *et al.* A phase I study of the left-shifting agent BW 12C79 plus mitomycin C and the effect on the skeletal muscle metabolism using 31P magnetic resonance spectroscopy. *Cancer Res* 1993; **53:** 5649–53.

Veratrine (14013-r)

Veratrine.

CAS — 8051-02-3 (mixture).

NOTE. Veratrine should be distinguished from protoveratrines obtained from veratrum.

A mixture of alkaloids from the dried ripe seeds of *Schoenocaulon officinale* (Liliaceae) (sabadilla).

Adverse Effects, Treatment, and Precautions

Veratrine resembles aconite (p.1542) in its action on the peripheral nerve endings and poisoning should be treated similarly. It is an intense local irritant and has a powerful direct stimulating action on all muscle tissues. It has a violent irritant action on mucous membranes, even in minute doses, and must be handled with great care. When ingested it causes violent vomiting, purging, an intense burning sensation in the mouth and throat, and general muscular weakness.

Uses and Administration

Veratrine should not be used internally. It was formerly applied externally for its analgesic properties and as a parasiticide, especially for head lice, but even when used in this way there is danger of systemic poisoning from absorption.

Vetrabutine Hydrochloride (12663-c)

Vetrabutine Hydrochloride *(BANM, rINNM).*

Dimophebumine Hydrochloride; Sp-281. *N,N*-Dimethyl-α-(3-phenylpropyl)veratrylamine hydrochloride.

$C_{20}H_{27}NO_2.HCl = 349.9$.

CAS — 3735-45-3 (vetrabutine); 5974-09-4 (vetrabutine hydrochloride).

Vetrabutine hydrochloride is a uterine relaxant.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Monzal†.

Vinburnine (14014-f)

Vinburnine *(rINN).*

CH-846; (–)-Eburnamonine; 3α,16α-Eburnamonine; Vincamone. (3α,16α)-Eburnamenin-14(15*H*)-one.

$C_{19}H_{22}N_2O = 294.4$.

CAS — 4880-88-0.

Vinburnine has been used in conditions associated with cerebral circulatory insufficiency.

Vinburnine phosphate has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Cervoxan; ***Ital.:*** Eburnal; Eubran†; Luvenil†; Scleramin; Tensiplex; ***Spain:*** Cervoxan; Eburnoxin.

Vincamine (14015-d)

Vincamine *(BAN, rINN).*

Methyl (3α,16α)-14,15-dihydro-14β-hydroxyeburnamenine-14-carboxylate.

$C_{21}H_{26}N_2O_3 = 354.4$.

CAS — 1617-90-9.

Pharmacopoeias. In *Belg.* and *Fr.*

An alkaloid obtained from *Vinca minor* (Apocynaceae).

Vincamine is claimed to increase cerebral circulation and utilisation of oxygen and has been used in a variety of cerebral disorders. Vincamine may have adverse effects on the cardiovascular system and care should be taken in patients with hypertension or cardiac dysfunction.

Vincamine salts including vincamine hydrochloride, oxoglurate, teprosilate, and hydrogen tartrate have also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Aust.: Aethroma; Cetal; Oxygeron; ***Belg.:*** Cerebroxine; Nooxine†; Pervincaminet†; ***Fr.:*** Oxovincat†; Pervincamine; Tripervant†; Vinca; Vincafor; Vincimax; ***Ger.:*** Angiopact†; Cetal; Equipur; Esberidin†; Ocu-Vinct†; Ophdilvas N; Vinca-Tablinen; Vincapront; ***Ital.:*** Anasclerol; Ausomina; Cerebraminat†; Dilart†; Encevint†; Pervint†; Roitent†; Teprosidet†; Vasonett; Vinca-Dil†; Vinca-Ri; Vinca-Treis; Vincadar; Vincafarm†; Vincafolina; Vincalen†; Vincamidol†; Vinsal; Vraap; ***Spain:*** Artensen†; Arteriovinca; Cerediant; Cetovinca; Dilarterial; Domeni†; Oxicebral†; Tefavinca; Vadicate; Vincacen; Vincamast†; Vincaminol; Vincavix†; ***Switz.:*** Aethroma; Cetal; Oxygeron; Pervincaminet†; Vinca minor†.

Multi-ingredient: ***Fr.:*** Rheobral; Vincarutine; ***Ital.:*** Bilancen†; ***Spain:*** Anacervix; Arteriobrate; Devincal; Dipervina.

Vinpocetine (14016-n)

Vinpocetine *(USAN, rINN).*

AY-27255; Ethyl Apovincaminate; Ethyl Apovincaminoate; RGH-4405. Ethyl (3α,16α)-eburnamenine-14-carboxylate.

$C_{22}H_{26}N_2O_2 = 350.5$.

CAS — 42971-09-5.

Vinpocetine 15 to 30 mg daily by mouth in divided doses has been used in cerebrovascular and cognitive disorders.

References.
1. Grandt R, *et al.* Vinpocetine pharmacokinetics in elderly subjects. *Arzneimittelforschung* 1989; **39:** 1599–1602.
2. Blaha L, *et al.* Clinical evidence of the effectiveness of vinpocetine in the treatment of organic psychosyndrome. *Hum Psychopharmacol Clin Exp* 1989; **4:** 103–11.

Preparations

Proprietary Preparations (details are given in Part 3)
Aust.: Cavinton†; Remedial†; ***Ger.:*** Cavinton; ***Jpn:*** Calan.

Vinyl Chloride (14017-h)

VCM; Vinyl Chloride Monomer. Chloroethylene.

$C_2H_3Cl = 62.50$.

CAS — 75-01-4.

Vinyl chloride is used in the manufacture of polyvinyl chloride (PVC) and other vinyl polymers. Occupational exposure to vinyl chloride in polymerisation plants has been associated with acro-osteolysis, especially in the terminal phalanges of the fingers, a condition resembling Raynaud's phenomenon, and sclerodermatous skin changes. Liver damage and hepatic angiosarcoma, splenomegaly, thrombocytopenia, impaired respiratory function, and chromosomal abnormalities have also occurred.

References.
1. Piratsu R, *et al.* La mortalità dei produttori di cloruro di vinile in Italia. *Med Lav* 1991; **82:** 388–423.
2. Infante PF, *et al.* Genetic risks of vinyl chloride. *Lancet* 1976; **1:** 734–5.
3. Mur JM, *et al.* Spontaneous abortion and exposure to vinyl chloride. *Lancet* 1992; **339:** 127–8.
4. Black CM, *et al.* Genetic susceptibility to scleroderma-like syndrome induced by vinyl chloride. *Lancet* 1983; **1:** 53–5.
5. Riordan SM, *et al.* Vinyl chloride related hepatic angiosarcoma in a polyvinyl chloride autoclave cleaner in Australia. *Med J Aust* 1991; **155:** 125–8.

Viquidil Hydrochloride (14019-b)

Viquidil Hydrochloride *(rINNM).*

LM-192; Mequiverine Hydrochloride; Quinicine Hydrochloride. 1-(6-Methoxy-4-quinolyl)-3-(3-vinyl-4-piperidyl)propan-1-one hydrochloride.

$C_{20}H_{24}N_2O_2.HCl = 360.9$.

CAS — 84-55-9 (viquidil); 52211-63-9 (viquidil hydrochloride).

Viquidil has been used in various cerebrovascular disorders as the hydrochloride in a daily divided dose of 200 to 300 mg by mouth.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Xitadil†; ***Ger.:*** Desclidium.

Water (7700-g)

Aqua; Aqua Communis; Aqua Fontana; Aqua Potabilis; Eau Potable; Wasser.

$H_2O = 18.02$.

CAS — 7732-18-5.

Purified Water (7701-q)

Aqua Purificata.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.viii), *Int.*, *Jpn*, *Pol.*, and *US*. *US* also includes Sterile Purified Water.

Some pharmacopoeias only include distilled water or have additional monographs for demineralised water or distilled water.

Purified water is prepared from suitable potable water either by distillation, by treatment with ion-exchange materials, or by any other suitable method. pH 5 to 7. **Store** in airtight containers which do not alter the properties of the water.

PREPARATION BY DEIONISATION. By passing potable water through columns of anionic and cationic ion-exchange resins, ionisable substances can be removed, producing a water of high specific resistance. Colloidal and non-ionisable impurities such as pyrogens may not be removed by this process.

PREPARATION BY DISTILLATION. In this process water is separated as vapour from non-volatile impurities and is subsequently condensed. In practice, non-volatile impurities may be carried into the distillate by entrainment unless a suitable baffle is fitted to the still.

Water for Injections (7702-p)

Aq. pro Inj.; Aqua ad Iniectabilia; Aqua ad Injectionem; Aqua Injectabilis; Aqua pro Injectione; Aqua pro Injectionibus; Eau pour Préparations Injectables; Wasser für Injektionszwecke; Water for Injection.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.viii), *Int.*, *Jpn*, *Pol.*, and *US*. *Br.* also includes Water for Irrigation and *US* also includes Sterile Water for Injection, Sterile Water for Inhalation, Sterile Water for Irrigation, and Bacteriostatic Water for Injection.

Water for Injections (Ph. Eur.) is distilled water free from pyrogens used to produce solutions for injection; it is prepared by distillation of potable water or purified water from a neutral glass, quartz, or suitable metal still fitted with an efficient device for preventing the entrainment of droplets; the first portion of the distillate is discarded and the remainder collected. Sub-monographs cover Water for Injections in Bulk and Sterilised Water for Injections.

Water for Injection (USP 23) is water purified by distillation or by reverse osmosis and contains no added substance. It is intended for use in parenteral solutions which are to be sterilised after preparation. Sterile Water for Injection (USP 23) is the subject of a separate monograph.

There are international standards for the quality of water intended for human consumption. Toxic substances such as arsenic, barium, cadmium, chromium, copper, cyanide, lead, and selenium may constitute a danger to health if present in drinking water in excess of the recommended concentrations. Water-borne infections are also a hazard.

Fluoride is regarded as an essential constituent of drinking water but may endanger health if present in excess—see Sodium Fluoride, p.742. Ingestion of water containing large quantities of nitrates may cause methaemoglobinaemia in infants; many countries have standards for nitrates in water.

The use of tap water containing metal ions (such as aluminium, copper, and lead), fluoride, or chloramine, for dialysis may be hazardous.

A hard water contains soluble calcium and magnesium salts, which cause the precipitation of soap and prevent its lathering and form scale and sludge in boilers, water pipes, and autoclaves. Temporary hardness in water is due to the presence of bicarbonates which are converted to insoluble carbonates on heating. Permanent hardness is due to dissolved chlorides, nitrates, and sulphates, which do not form a precipitate on heating. The presence or absence of such salts can play a part in cardiovascular health.

Without further purification, potable water may be unsuitable for certain pharmaceutical purposes. In such instances, purified water should always be used. Most pharmacopoeias include monographs on various preparations of water, such as water for injection or injections. Potable water should not be used when such preparations of water are specified.

Excessive ingestion of water can lead to water intoxication with disturbances of the electrolyte balance.

Wild Carrot (13990-c)

Dauci Herba; Daucus.

Pharmacopoeias. In *Chin.*

The fruits of the wild carrot, *Daucus carota* (Umbelliferae) have been used as a diuretic and anthelmintic, and are included in herbal preparations for various indications. Other parts of the plant have been used in folk medicine. The root of the cultivated form is a culinary item and a source of carotenoids in the diet.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Infectodyspept.
Multi-ingredient: ***Ital.:*** Pluriderm; ***UK:*** Sciargo.

Wild Cherry Bark (2418-w)

Prunus Serotina; Virginian Prune; Virginian Prune Bark; Wild Black Cherry Bark; Wild Cherry.

The dried bark of the wild or black cherry, *Prunus serotina* (Rosaceae), known in commerce as Thin Natural Wild Cherry Bark, containing not less than 10% of water-soluble extractive. It has a slight odour and an astringent, aromatic, bitter taste, recalling that of bitter almonds. It contains (+)-mandelonitrile glucoside (prunasin) and an enzyme system, which interact in the presence of water yielding benzaldehyde, hydrocyanic acid, and glucose.